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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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SURGERY

VOL. 33 MARCH, 1953 NO. 3

Original Communications

THE TREATMENT OF INTRACRANIAL AND CRANIAL SUPPURATION WITH REFERENCE TO THE LOCAL AND SYSTEMIC USE OF BACITRACIN

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SINCE our first report[1] of 61 consecutive patients with neurosurgical infections, who were treated with bacitracin and other antibiotics, another 14 patients have been similarly treated in different hospitals and the results are presented herewith. While this is a relatively small group, it seems to be worthy of presentation at this time because the cases illustrate suppurations involving the different layers of the intracranial contents, from the ventricular system outward as well as the cranium itself and the overlying soft parts. The variety of these lesions including the treatment used and the results obtained are shown in Table I.

In this series there are 3 cases of brain abscess representing 3 different types, 1 a so-called paradoxical cerebral abscess, 1 a frontal lobe abscess arising from infection of the paranasal sinuses, and the third a metastatic lesion from a putrid lung infection. A fourth patient had suppuration in the subdural space as well as an abscess in the cerebrum. Five cases were of patients with meningitis. One of these was due to the meningococcus, one was caused by a *Staphylococcus aureus,* and a third was due to a *Streptococcus hemolyticus* involving both the ventricular system and the leptomeninges. Two patients had postoperative aseptic meningitis following a high cervical laminectomy. One had a fungation of the brain following a compound fracture of the skull. In these 3 cases bacitracin was used as a prophylactic. Four patients were treated for an infected craniotomy wound. In one of these the infection was limited to the scalp and the underlying soft tissue without bone involvement while 3 developed a chronic osteomyelitis of the bone flap. All but 1 of these 14 patients received

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The bacitracin, used in the cases reported, was produced by the Commercial Solvents Corporation, Terre Haute, Ind., by Chas. Pfizer & Co., Inc., Brooklyn, N. Y., and by S. B. Penick & Co., New York, N. Y.

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TABLE I. CASES OF DIFFERENT KINDS OF CRANIAL AND INTRACRANIAL SUPPURATION TREATED WITH BACITRACIN

NATURE OF SUPPURATION	NO. OF CASES	BACITRACIN, ROUTES OF INJECTION	RESULT
Brain abscesses	3		
Paradoxical brain abscess	1	Intracerebral, intrathecal, epi- and subdural and intramuscular	Recovery
Brain abscess secondary to paranasal infection	1	Intracerebral, intrathecal, epi- and subdural and intramuscular	Recovery
Metastatic brain abscess from lung abscess	1	Intracerebral, intrathecal, epi- and subdural and intramuscular	Recovery
Subdural empyema and intracerebral abscess	1	Intracerebral, epi- and subdural	Recovery
Meningitis	5		
Staphylococcus aureus meningitis	1	Intrathecal and intramuscular	Death
Hemolytic streptococcic meningitis	1	Intrathecal, intraventricular, into the ventriculocisternostomy tube	Recovery
Meningococcic meningitis	1	Intrathecal and intramuscular	Recovery
Postoperative aseptic meningitis	2	Intrathecal and intramuscular	Recovery
Compound fracture of skull with cerebral fungation	1	Intracerebral, sub- and epidural, and intramuscular intrathecal	Recovery
Infected craniotomy wound	4		
With no involvement of bone	1	Local and intramuscular	Rapid wound healing in all
Chronic osteomyelitis of bone flap	3	Epidural and intramuscular	
Total	14		

bacitracin intramuscularly, and all received local bacitracin either into the ventricles, into the brain tissue, into the subarachnoid, subdural, or epidural space, or into the soft tissue overlying the bone flap. All but 1 of these patients responded favorably. The only fatal outcome was in the case of the patient with staphylococcus meningitis who died from gastrointestinal and pulmonary complications.

BRAIN ABSCESS

The use of bacitracin in the treatment of cerebral abscess is illustrated by the following case:

CASE 1.—E. B. S., a 30-year-old woman, was admitted to the Mount Sinai Hospital with a diagnosis of Eisenmenger's complex, *Staphylococcus aureus* septicemia, and left occipital lobe abscess.

The patient was born a "blue baby." All her life, she had led a sheltered existence in her parents' house. Walking about one to two blocks produced extreme exertional dyspnea. However, she never had any episode of congestive cardiac failure.

About ten days before admission, following a day of diarrhea, she developed a low grade fever, rising as high as 101.6° F. She began to see multicolored light spots in both eyes. This persisted for five or six days. Then she found that she was unable to see well with her right eye.

Examination showed that the patient was deeply cyanotic, with clubbed fingers and toes, and dyspneic on walking. The temperature was 100.6° F., the pulse rate 100, and the

respiration rate 22 per minute. The blood pressure was 100 to 105 systolic. The diastolic was not determined. On percussion the cardiac apex was about 2 cm. lateral to the left midclavicular line. In the left lateral recumbent position, a low-pitched presystolic murmur was heard at the base. P_2 was greater than A_2 and P_1 was split. Examination of the oral cavity revealed extensive pyorrhea and gingivitis.

Neurological examination showed a right homonymous hemianopsia. The patient was euphoric and slightly confused as to time and space.

Laboratory findings included white blood cells 7,000 with 81 per cent polymorphonuclear leukocytes, red blood cells 5.8 million, hemoglobin 20.4 Gm., and blood urea nitrogen 16. Blood culture grew a *Staphylococcus aureus A* which was sensitive to both penicillin and bacitracin. From the mouth a swab culture disclosed a *Staphylococcus albus* and a *Streptococcus viridans*. Radiographic examination of the jaw revealed advanced periodontal destruction of bone with deep pocket formation. Electro-encephalogram located a slow focus in the left occipital region. Electrocardiographic changes indicated an enlargement of the right ventricle and auricle.

On the fifth day after admission, a lumbar puncture was performed. The cerebrospinal fluid was clear and colorless, with an initial pressure of 210 mm. It contained 28 mg. per cent of total protein and W.B.C. 94. Because the patient said that she was sensitive to penicillin, she was treated with terramycin, 3 Gm., and Gantrisin, 2 Gm. a day. On the third day of this treatment without improvement, these drugs were replaced by bacitracin which was given 20,000 units every 6 hours by the intramuscular route.

On the twelfth day, a bilateral papilledema made its appearance. The right pupil was larger than the left. Deep tendon reflexes were exaggerated on the right with a sustained right patellar and ankle clonus. Slight weakness developed in the right upper limb. The right upper abdominal reflex disappeared. The patient became lethargic and vomited repeatedly.

On the following day, through a left parieto-occipital bone flap, an encapsulated abscess, containing about 30 c.c. of thick yellowish green pus, was removed from the left occipital lobe. During the process of dissection, the thin capsule was accidentally ruptured and pus was spilled over the wound. After the evacuation of the abscess, Gelfoam soaked in bacitracin solution in a concentration of 5,000 units per cubic centimeter was used to cover the wall of the cerebral wound. This served the purpose of both hemostasis and antisepsis. The wound was closed in layers with silk. The total amount of bacitracin used in the cerebral wound was 50,000 units. In addition to this amount, another 10,000 units in 2 c.c. of normal saline was instilled under the scalp after the closure of the wound. Postoperatively, 20,000 units of bacitracin in 4 c.c. of physiologic saline was injected into the lumbar subarachnoid space as a prophylactic. Culture of the abscess showed no growth although direct smear disclosed gram-positive cocci.

The temperature became normal on the second postoperative day and stayed so for three days. The wound healed per primam. On the fourth day systemic bacitracin was reduced to 10,000 units every six hours for three days and then the previous dosage was resumed. It was discontinued on the forty-second day.

However, in spite of the antibiotic therapy, the patient continued to run a low grade fever. Therefore, it was decided to eliminate the foci of infection. Twenty-four teeth were extracted and three scalings were performed in a period of eight days, twelve days after the craniotomy. After bacitracin had been stopped, procaine penicillin was given by the intramuscular route, 1,200,000 units daily for six days, and then double the dosage for fourteen days until the time of discharge, at which time the temperature had been normal for two weeks. This disproved the patient's story of allergy to penicillin.

During the course of bacitracin therapy, the noncatheterized urine showed a trace or one plus albumin with a few white blood cells occasionally in small clumps. There was no change in blood urea nitrogen.

This case illustrates that the extensive local use of bacitracin on the central nervous system will produce no untoward toxic effect. The total amount was

80,000 units, 50,000 in the cerebral wound, 10,000 under the sutured scalp, and 20,000 units into the lumbar subarachnoid space.

Metastatic brain abscess of this type is rare. This is the fourth case of a so-called paradoxical brain abscess with survival recorded in the medical literature.[2-4] The result in this case can be called good with minimal signs of nephrotoxicity.

One case of subdural empyema associated with an intracerebral abscess in the right frontoparietal region and 2 other cases of brain abscess, 1 a right frontal lobe abscess originating from paranasal sinusitis and the other a metastatic abscess secondary to a putrid lung infection, were all similarly treated with systemic and local bacitracin. In the former case the causative organism could not be recovered from the abscess and its content. From the abscess of the latter case, an anaerobic gram-positive streptococcus was cultivated. This abscess was found not encapsulated and its removal was incomplete. Therefore, the cerebral wound was drained with a rubber tube for ten days and through this tube 10,000 units of bacitracin was injected daily until it was removed. The wound was completely healed two days later.

The postoperative course in all 3 cases was uneventful and none showed any untoward effect from the local administration of bacitracin.

MENINGITIS

Three patients with bacterial meningitis were treated with bacitracin; 2 survived and 1 died. One patient had a meningococcic reinfection of the leptomeninges from an undisclosed focus. In spite of combined treatment with sulfadiazine, penicillin, streptomycin, and Chloromycetin for fifteen days, the temperature remained septic and the patient gradually developed a right-sided hemiplegia with generalized convulsions and became comatose. The blood urea nitrogen was 68 mg. per cent. Regardless of the renal damage caused by sulfadiazine, because of the severity of the infection, bacitracin was given both by the intrathecal and by the intramuscular route for fourteen and eighteen days, respectively. The bacitracin not only produced no further injury to the kidney but the blood urea nitrogen fell abruptly from 68 to 12 mg. per cent during the course of bacitracin therapy. The patient made a complete recovery. This case was briefly described in another article.[5]

The only mortality of this group was in an aged, arteriosclerotic, and hypertensive patient, who developed a *Staphylococcus aureus* meningitis following a left spheno-ethmoidotomy and antrotomy. In spite of the treatment with penicillin, streptomycin, and Aureomycin for two days, he became comatose. Then bacitracin was called upon and was given, 10,000 units every four hours by the intramuscular route and 20,000 units twice a day intrathecally for two days and 10,000 units daily for another two days. The temperature came down to normal and the patient became increasingly responsive. The cell count of the cerebrospinal fluid dropped from W.B.C. 3,200 to 300. However, in spite of this, the patient suddenly died the next morning. Autopsy findings showed a perforation of the cribriform plate, acute ulcerations of the duodenum with

hemorrhage in the intestinal tract, and atelectasis of the right lung. Microscopic examination of the brain and the meninges revealed that there was no evidence of an acute suppuration.

The history of the case of streptococcic meningitis is briefly presented as follows:

CASE 2 (Bacitracin Study No. 1271).—A 15-year-old girl was admitted to the Beth Israel Hospital, New York, N. Y., with a diagnosis of medulloblastoma cerebelli. Following a ventriculogram, a suboccipital exploratory craniotomy was performed and the cerebrospinal fluid circulation was found blocked at the fourth ventricle. A Torkildsen procedure was carried out. Postoperatively, the patient ran a septic temperature, ranging from 99° to 104° F. Culture of the blood showed no growth. A variety of antibiotic agents were administered, namely, procaine penicillin, 300,000 units twice a day for eighteen days, and Aureomycin 250 mg. every six hours for five days. The latter was then replaced by Chloromycetin in the same amount for nine days. Then terramycin was tried in the same dosage for twelve days. In spite of this treatment, the patient's temperature remained septic.

On the twenty-sixth postoperative day, the patient became lethargic and vomited repeatedly. The neck became stiff. A lumbar puncture was made, yielding cloudy cerebrospinal fluid with W.B.C. 380. On the next day her condition became worse. Culture of the cerebrospinal fluid revealed a *Streptococcus hemolyticus*. The occipital wound was found tense, fluctuating, and tender on palpation. It was aspirated and turbid fluid was obtained. Culture of this fluid grew a *Streptococcus hemolyticus* and a *Staphylococcus aureus*. Laboratory tests showed that both organisms were sensitive to bacitracin but resistant to penicillin, Aureomycin, terramycin, and Chloromycetin, and there was no synergistic action between penicillin and bacitracin. In desperation but with the thought that it might turn the tide, bacitracin was added to the therapy. Eight thousand units was given every four hours by the intramuscular route and 10,000 units in 4 c.c. of physiologic saline was instilled once daily by the intrathecal route. Two days later, the dosage of intramuscular bacitracin was changed to 10,000 units every six hours and was continued for sixteen days.

Because of the repeated vomiting, it was thought that the ventriculocisternostomy tube had filled with clot. On the thirtieth postoperative day, the tube was punctured through the skin and it was found patent. Into this tube, 10,000 units of bacitracin was injected after some cloudy fluid had been removed. Culture of this aspirated fluid grew the same organisms. On this day, another 20,000 units of bacitracin was instilled into the lumbar subarachnoid space.

A ventricular puncture was made next day. The ventricular fluid was found cloudy, containing 2,850 polymorphonuclear neutrocytes but culture of the fluid showed no growth. Through the ventricular needle, 20,000 units of bacitracin in 4 c.c. of physiologic saline was injected into the right lateral ventricle. The patient showed marked signs of improvement on the following day, particularly with regard to consciousness. She was alert and at times irritable. The temperature dropped from 104° and 105° F. to 100° and 102° F. The intraventricular and intrathecal therapy with bacitracin in the aforementioned dosage (20,000 units) was repeated. One day later, 10,000 units of this antibiotic was injected into the Torkildsen tube by means of a percutaneous puncture. Thereafter, the condition of the patient improved steadily and she became well oriented. The next day, 55 c.c. of turbid fluid was removed from the left side of the wound by aspiration and into the wound 10,000 units of bacitracin was instilled.

The wound opened spontaneously on the following day, and drained a large amount of xanthochromic fluid. The temperature became normal. Thereafter, the local antibiotic therapy was discontinued. The wound was dressed daily with plain gauze and was completely healed ten days later. Systemic bacitracin was continued for another three days and then was stopped. Chloromycetin and procaine penicillin were discontinued four and nine days later, respectively. In order to avoid injections, terramycin, 250 mg. every six hours,

was administered for seven days after penicillin had been stopped. During the course of bacitracin treatment, the urine at times showed a trace to one plus albumin and occasional white blood cells, but the blood urea nitrogen was normal.

At the time of discharge from the hospital eighteen days later, the patient's temperature was normal. Fundoscopic examination showed that the eye grounds were flat on both sides. Judging from the absence of clinical symptoms, the ventriculocisternostomy tube probably remained functioning.

Too many antibiotics participated in the therapy of this case making it difficult to evaluate the effectiveness of any particular one. But inasmuch as the laboratory tests indicated that the causal organisms were resistant to all of the antibiotics used except bacitracin, it seems reasonable to conclude that this was the curative agent. Bacitracin was used locally by direct instillations into the ventricle, the lumbar subarachnoid space, and the ventriculocisternostomy tube. It produced no irritating effect on the central nervous system and, in fact, inasmuch as improvement only began after its initiation, it would seem that bacitracin played a major role in the control of the infection both of the leptomeninges and of the ventricles. Furthermore, the ventriculocisternostomy tube, which was vitally important in maintaining the cerebrospinal fluid circulation in this case, did not require removal and it remained functioning.

INFECTED CRANIOTOMY WOUNDS

During this period, 4 patients with infected craniotomy wounds were encountered in different hospitals and the authors were called in consultation. In one case infection occurred in a right frontotemporal craniotomy wound on the fourth postoperative day. Culture of the wound yielded a *Staphylococcus aureus* which was resistant to penicillin but sensitive to bacitracin. This wound was treated by local instillations of 10,000 units of bacitracin in 2 c.c. of normal saline daily for twelve days, supplemented by systemic injections of bacitracin, 10,000 units every eight hours for ten days, and procaine penicillin, 300,000 units twice a day for fifteen days. The wound was completely healed after the 12 local injections of bacitracin.

In 3 cases of chronic osteomyelitis of the skull resulting from an infected craniotomy wound of three and one-half, four, and ten months' duration, bacitracin was used both locally and systemically as supplementary therapy to the surgical removal of the infected soft tissues and the osteomyelitic bone. The causative organisms were found to be a *Staphylococcus aureus* in 2 and *Staphylococcus albus* in 1 case. The former organisms were resistant to penicillin but susceptible to bacitracin, and there was a synergistic action in vitro with penicillin and bacitracin in both instances. The *Staphylococcus albus* was moderately resistant to penicillin but sensitive to bacitracin and there was no synergism between these 2 antibiotics.

The dosage of systemic bacitracin used in these 3 cases is similar to the dosage for the treatment of other infections. These patients were given 10,000 units of bacitracin every six to eight hours and procaine penicillin, 300,000 units once or twice daily for a week or ten days after the wound had been completely healed. The local therapy included: (1) preoperative instillations

of 10,000 to 20,000 units of bacitracin in 1 or 2 c.c. of normal saline into the discharging sinus, once or twice a day, depending upon the condition of the wound, (2) the deposition of the same amount of bacitracin in the wound after the removal of the diseased tissues at the operation, and (3) postoperatively, in the first two days, one or two injections of 10,000 units of bacitracin into the sutured wound whenever it was deemed necessary. Following this treatment, the wound healed rapidly in all 3 cases.

THE PROPHYLACTIC USE OF BACITRACIN IN NEUROSURGICAL PATIENTS

In 3 patients bacitracin was used as a prophylactic. Two patients developed a postoperative acute aseptic meningitis,[6] following a high cervical laminectomy in one and a craniospinal exploration in the other. In both patients, the repeated direct smears and cultures of the cerobrospinal fluid showed no organisms. Therefore, they were classified in the category of postoperative acute aseptic meningitis and bacitracin was given both by the intramuscular and by the intrathecal route as a prophylactic. One patient received 8 and the other 4 intrathecal injections of bacitracin (10,000 units daily). Both patients recovered and showed no untoward effect. A third patient sustained a compound fracture of the skull of the right parietal region with cerebral fungation. The contaminated wound was immediately débrided. The scalp, the bone edges, and the lacerated dura were trimmed and the devitalized brain tissue was removed by suction. Into the cerebral wound, 15,000 units of bacitracin was deposited and the scalp was closed in layers with silk. Another dose of 5,000 units was instilled beneath the sutured scalp. The patient was also given systemic bacitracin and procaine penicillin for ten and nine days, respectively. The local application of bacitracin to the cerebral wound produced no toxic effect. The wound healed per primam.

DISCUSSION

From the study of these cases, we are struck by two things: (1) the failure of treatment following the indiscriminate use of the antibiotics in the early handling of the case, and (2) the successful outcome when the appropriate antibiotic was used.

Sometimes when a patient is very ill, the doctor in charge of the case, in a panic or at the behest of the patient or the family, will start treatment with a whole battery of antibiotics in the hope that one of them will stop the infection promptly. Often he does not take the opportunity of finding out the causative organism, or, if he does, he fails to test its sensitivity to the available antibacterial agents. This is neither intelligent nor scientific, and it often fails to accomplish its purpose.

We now have 8 potent antibiotics which have demonstrated their ability to control infections caused by susceptible organisms when these agents are applied either locally at the site of inflammation or systemically by intramuscular or oral administration. However, they are only effective when the causative organism is susceptible. The methods for determining this susceptibility are reliable and fairly simple.

The only way to give the patient the full benefit of our present knowledge is to determine the causative organism as soon as possible, test for sensitivity, and then give the antibiotic or combination of antibiotics which are indicated by the results of these tests. It is reasonable, of course, to start with the antibiotic which the clinician's experience tells him is most likely to succeed, but this should not persuade him to neglect taking cultures or changing treatment if the results of the tests clearly indicate that he should do so.

Brain Abscess in Congenital Heart Disease.—To date, the clinicopathologic literature contains 52 instances[2-4, 7-11] of cerebral abscess in association with the tetralogy of Fallot, Eisenmenger's complex, auricular septal defect, ventricular defect, or a rudimentary right ventricle with both auricles emptying into the left ventricle. Between the years 1938 and 1947, 105 cases with cerebral abscess were autopsied at the Los Angeles County Hospital. Eleven of these were associated with congenital heart disease.[2] Ruhberg[9] found that a paradoxical abscess occurred once for every 13 cases of metastasis from lung abscess. Hanna[10] recorded 6 cases of metastatic brain abscess in 160 fatal cases of congenital cardiac disease. Robbins[11] found 3 in 53, and Abbott's finding was 7 in 1,000.[12]

Among these 52 reported cases of paradoxical brain abscess, only in 6[2-4, 13, 14] was a clinical or ante-mortem diagnosis of cerebral suppuration made and only 4 patients,[2-4] including this one of ours (Case 1), survived the infection.

An accurate clinical diagnosis is difficult to reach in such instances. Low grade fever and neurological signs, such as mental changes, hemiparesis, hemianesthesia, as well as a change of the visual field and cerebrospinal fluid, are not uncommon in patients with congenital heart disease with or without circulatory infection, especially during their late stages. These signs could be caused by thrombosis or embolism of the cerebral vessels as a result of polycythemia, which is commonly associated with congenital heart disease. Even the papilledema is not a pathognomonic sign. It has been found occasionally in cases of extensive cerebral vascular thrombosis which has been proved either at autopsy or at operation. However, when a positive blood culture is obtained in a patient with congenital heart disease who has developed neurological symptoms such as those described, a paradoxical abscess should be suspected. The other laboratory tests such as electro-encephalogram and an air study or an arteriogram are indicated, and the intracranial cavity should be explored accordingly.

Before the advent of penicillin, no survival was recorded in the medical literature. It was not until 1946 that Smolik and associates[2] reported the first survival case of a paradoxic brain abscess. Cohen and his associates[3] and Beller[4] recorded 2 more cases in 1951. Case 1 of the present communication is herewith recorded as the fourth.

Metastatic Brain Abscess of Pleuropulmonary Origin.—Gates and associates[15] found that, in 104 cases, metastatic brain abscesses were associated with pleuropulmonary disease in 42 (41 per cent). In 62 per cent of 326 cases of metastatic brain abscesses reported, both from the literature and from the records of the Mayo Clinic, the abscesses were single.

Until the discovery of penicillin, the mortality from metastatic brain abscess was almost 100 per cent. Cohen[16] and Cohen and Drooz[17] reported 18 proved cases of metastatic brain abscesses of pleuropulmonary origin, of which none survived. In his review of literature in 1936, King[18] could find only 8 cases in which metastatic brain abscess had been cured by surgery. In 1946, Sachs reported 52 deaths in 108 operated cases of brain abscess. Excluded from this series were 20 patients with metastatic brain abscess of thoracic origin, of whom 19 died.[19] Pennybackek[20] also reported 11 deaths in 12 cases of abscesses of this nature.

Probably, this high mortality in thoracicogenic brain abscesses might be explained on the basis that the primary focus of infection has already debilitated the patient and the infecting organisms which are often anaerobes, were more virulent and more necrotizing and prevented the formation of a capsule. It is known that when anaerobic and aerobic organisms exist in symbiosis in a brain abscess the process of encapsulation is delayed. Charrier and Ferradou[21] stated that a capsule is never found with anaerobic bacteria. This formation of a capsule is greatly desired by neurosurgeons. Gates and associates found that 52 per cent of their 104 patients died in the first 14 days of their illness and in 41 the abscess had ruptured into a ventricle.[15]

Nowadays, with the use of antibiotics, pessimism is no longer justified. Rizzoli and his associates, in 1948,[22] reported 10 consecutive cases (7 of them were thoracicogenic) cured after surgical intervention and antibiotic therapy.

In the case of pulmogenic cerebral abscess of this series, the brain lesion was secondary to a long-standing lung infection. The culture of the contents showed an anaerobic streptococcus and at the operation, the abscess was found completely nonencapsulated. The surgical extirpation of the focus with extensive local application of bacitracin, supplemented by systemic antibiotics, effected a cure.

Brain Abscess Secondary to Infection of the Cranial Bones.—The majority of cases of cerebral abscess are secondary to suppuration of the cranial bones, the sinuses, or the middle ear. Therefore, the location of these abscesses is limited to the part of the brain which is adjacent to the infected structure. They are almost always solitary and are not associated with systemic infection or a debilitating primary focus as in the case of metastatic abscesses. The outcome of surgical treatment in this type of abscesses has usually been more favorable than in the metastatic ones, even before the days of antibiotic therapy. This article contains only one such case.

Meningitis.—Prior to the advent of sulfonamides and penicillin, septic meningitis was a fatal disease. The mortality ran well over 90 per cent.[23] Excluding 1 in which the meningitis was caused by a meningococcus, there were 16 cases of septic meningitis included in our bacitracin series. Thirteen of these 16 cases have been previously reported.[24, 25] The causative organisms were staphylococcus in 7, streptococcus in 3, pneumococcus in 2, a mixture of organisms in 2, and an unidentified gram-positive coccus in 2 patients. In uncomplicated cases, the infection usually responded well to bacitracin therapy

by daily intrathecal injection of 10,000 to 20,000 units. In many cases, however, this local treatment was supplemented by the intramuscular use of bacitracin with or without some other antibiotic whenever it was deemed necessary. Of these 16 treated patients, 5 died from complications.

In this series there is only 1 patient with meningococcic meningitis treated with bacitracin and he recovered after other therapeutic agents had failed.

Case 2 represents a second incidence of wound infection with septic meningitis following a Torkildsen procedure and a suboccipital decompression. The first case has been previously reported.[24] Patients in both cases were treated with bacitracin by the intrathecal and intraventricular injections and with the ventriculocisternostomy tube in the infected field. The tube in the second case remained functioning after the infection had been cleared.

Infected Neurosurgical Wounds and Chronic Osteomyelitis of the Skull.—In spite of modern aseptic technique and the extensive use of penicillin as a preoperative and postoperative prophylactic, wound infection still occurs and not infrequently. The causative organism, in such instances, is often found to be a penicillin-resistant staphylococcus. The incidence of penicillin-resistant strains of this organism is from 43[5] to 53 per cent.[26] In 449 strains of coagulase-positive *Staphylococcus aureus,* 55.9 per cent were found to be resistant to penicillin, while 97.3 per cent were sensitive to bacitracin.[5] This, probably, accounts for the frequent failure of penicillin in prophylaxis or in active therapy or in both.

Infection of a craniotomy wound is a serious matter. When it occurs, it almost always involves the epidural space, the bone flap, and frequently the structures underlying the dural covering. The bone flap, which has already been deprived of its blood supply completely or partially by the operation, like a bone graft, cannot resist the infection. Therefore, it generally has to be removed in order to permit a complete and rapid healing of the infected wound. In the present series in 1 case, the bone flap was saved by repeated local instillations of bacitracin solution. In the remaining instances, the bone flap was either completely or partially removed. In 9 cases thus treated with surgery and bacitracin, the wound healing was rapid and complete in all.[1]

Contaminated Neurosurgical Wounds.—Since bacitracin is far less toxic than penicillin when applied directly to the central nervous system,[27, 28] we believe that it is safe to administer bacitracin to any craniotomy when contamination is suspected. The intrathecal, intracisternal, and intracerebral, as well as intraventricular, injections of bacitracin have produced no convulsion, paralysis, or radiculitis.[1]

SUMMARY

1. Seven cases of intracranial suppurations, 3 brain abscesses, 3 septic meningitis, and 1 subdural empyema associated with an intracerebral abscess, and 4 patients with infected craniotomy wound, 3 of whom had a chronic osteomyelitis of the skull, were treated with local, intrathecal, intracerebral,

or intraventricular bacitracin either with or without intramuscular bacitracin. Of these 11 patients, 1 died from gastrointestinal and pulmonary complications. All the others survived.

2. Bacitracin was used as a prophylactic in 3 patients, 2 with acute postoperative aseptic meningitis and 1 with a compound fracture of the skull resulting in cerebral fungation. This antibiotic was administered intrathecally in the former cases and intracerebrally in the latter.

3. The application of bacitracin directly into and on the surface of the central nervous system has produced no untoward effects.

4. From our experience it would seem that bacitracin is the antibiotic of choice for neurological infections because (A) the organisms are usually sensitive to bacitracin, (B) there is no toxicity observed following the local application of bacitracin solution into the ventricles, to the infected area of the brain, or into the subarachnoid space.

5. Shotgun antibiotic therapy is not intelligent therapy. The organism should be recovered as soon as possible and tests made for sensitivity in order to find out the most effective antibiotic and to render adequate treatment at the earliest possible time.

6. Bacitracin is a logical antibiotic for prophylactic use in contaminated neurosurgical wounds.

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STUDIES ON INTRAHEPATIC ARTERIAL CIRCULATION

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UNEXPLAINED sequelae still complicate surgery of the gall bladder and bile passages. The paucity of studies on circulation of the liver could indicate that the anatomy was completely explored and understood; yet some postoperative phenomena have a definite vascular origin. Dr. I. S. Ravdin suggested that the arteries of the liver be restudied to see whether the arterial anastomoses in the liver were as adequate as commonly believed.

The careful study of Martens[1] led to the conclusion that "between the liver arteries there are always fine anastomoses either between the peripheral branches within the liver or by way of the capsular blood vessels. A certain number of cases show typical huge intrahepatic arcades between the right and left ramus located close to the hilus." Until very recently this was the only modern study, and it is still the only comprehensive survey of the liver arteries.* The excellent demonstrations of Hans Elias[2] have added clarity to many details of the subject. Martens' conclusions, while widely accepted, have neither been confirmed nor refuted. The studies reported here, using methods similar to Martens', led to totally different conclusions. With the use of his exact technique, Martens' specimens can be duplicated and his conclusions justified. However, a critical refinement of the Martens technique discloses an entirely different pattern. His method, although apparently adequate, did not provide for certain peculiarities of the hepatic circulation.

Our preliminary studies were made on embryo pigs because of their availability. The aorta was injected with a color mass, then the hepatic arteries were dissected. The specimens did not yield useful results because of lack of specificity of injection. The livers of the dogs used in a study on experimental injuries to the common duct[3] were next used, primarily to perfect technique. These preliminary studies gave us a familiarity with numerous masses of varying densities and viscosities. From among these one was chosen which proved to be most suitable for our purpose.

TECHNIQUE

Many injection masses whose characteristics were well known were available in our laboratory. Likewise, the several techniques suitable for demonstration of vascular pattern are in common use here. Of all of these, such as corrosion preparations, transparent preparations and the like, the demonstration by roentgen film seemed best suited for our study.

This report is part of a study presented to the Graduate School of Medicine of the University of Pennsylvania, in partial fulfillment of requirements for the degree of Master of Medical Science.

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*Petren *Die Venen der Gallenblase*, as its title indicates, deals only with the veins of the gall bladder.

Fig. 1.

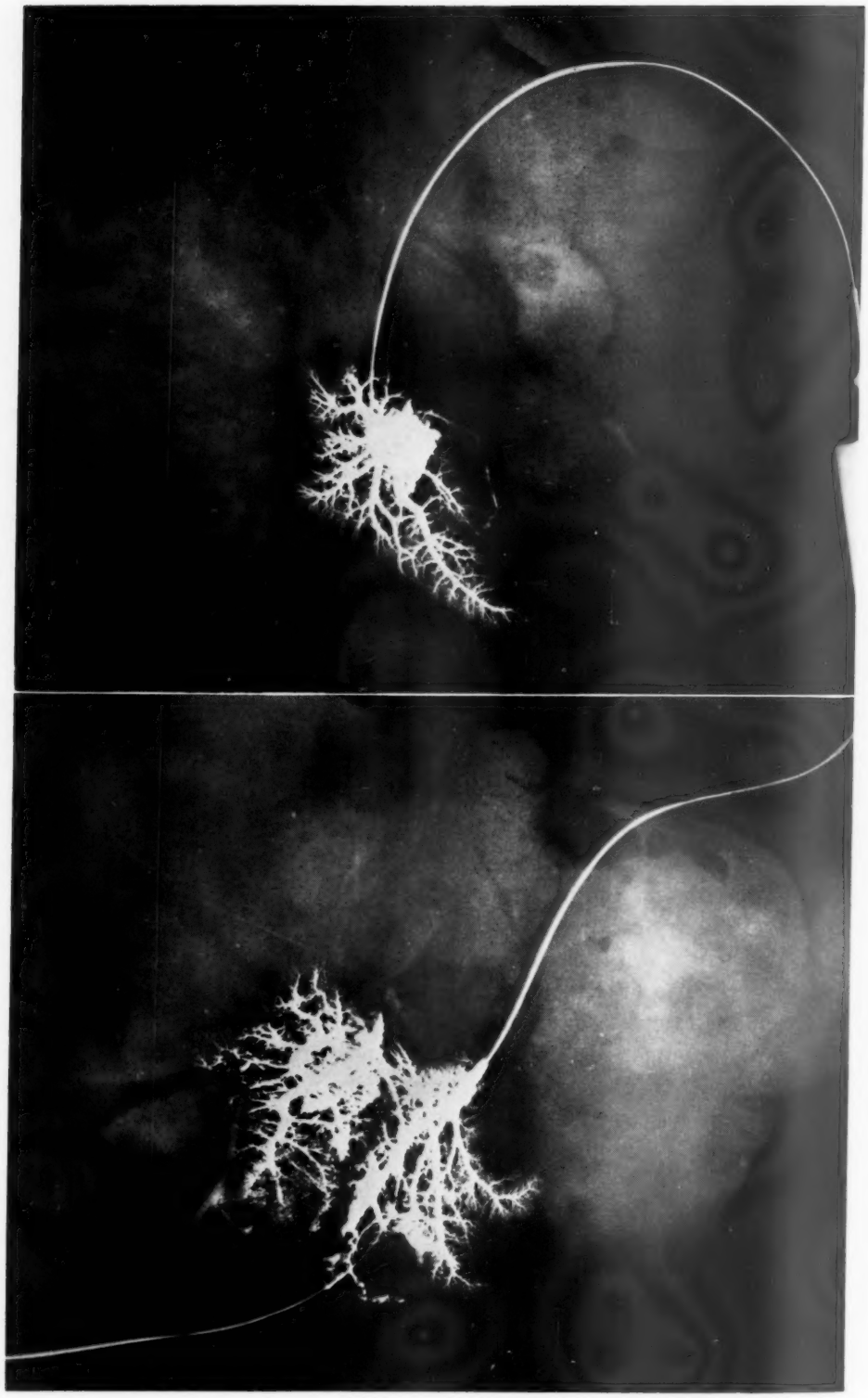

Fig. 2.

Fig. 1.—Roentgenogram of a fresh human liver in which radiopaque material was injected into a small branch of the hepatic artery entering at the hilus. A single pyramidal lobe is outlined.

Fig. 2.—The same liver as in Fig. 1 x-rayed after a second such vessel has been injected.

Selecting among the masses, a suspension of cinnabar (mercuric sulfide) was chosen. It has high tinctorial value, dense roentgen opacity, and may be obtained in particle size under seven microns. We used Weber's Artist Watercolor Vermillion. This is largely finely divided cinnabar in a gum base. The size of vessel filled is determined by the water dilution, i.e., consistency, and not by the particle size, since the particles are ground so fine. A "coarse mass" of the early workers would be a thick mass. We thinned ours to the liquidity of a low fat content milk. This mass in the ordinary hypodermic syringe and with light thumb pressure fills vessels down to the precapillary size. In this dilution, with proper regard for kilovoltage, the mass will cast a roentgen shadow in even the finer vessels. The plastic tube referred to below was originally obtained from a purveyor of insulating materials. Similar tubes are now readily available through surgical supply dealers.

Fig. 3.—The same liver as in Fig. 1 showing the x-ray appearance after a third small hilar vessel was injected.

Many papers detail the anomalies of the hepatic artery.[4-12] I had the good fortune to review personally Michels'[11] material with him. During the demonstration he called my attention to the many smaller branches entering at the hilus, as many as twenty or more. We thought we might make use of these arteries for injection. Unexpected results were obtained. The method was one employed successfully in the Anatomy Laboratory in studies on the coronary circulation in the heart.[13] A small catheter-like plastic tube was inserted into one of these arteries at the hilus, and pushed along until it was wedged tight in the lumen of the artery. The tube had an outside diameter of 1.4 mm., and its tip had been slightly rounded by heat.

When a roentgenopaque mass was injected a result such as shown in Fig. 1* was obtained. The artery here is obviously an end-artery, supplying only one pyramidal lobule.

*Photographic reproductions of roentgenograms were made by Alex Vaskelis.

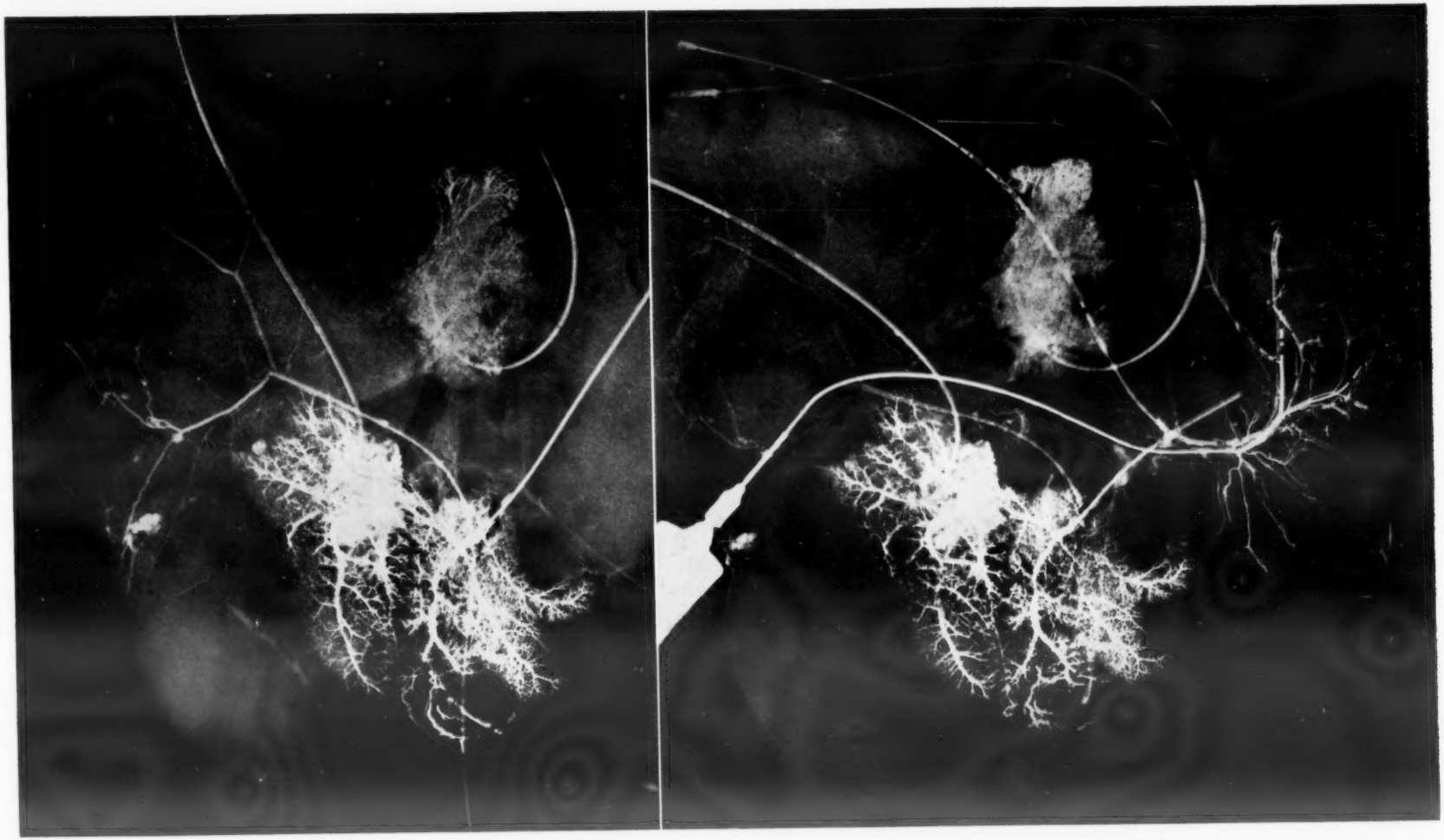

Fig. 4.

Fig. 5.

Fig. 4.—The same liver as in Fig. 1 after the right hepatic artery was injected just at the liver porta.
Fig. 5.—The same liver as in Fig. 1 after a small hilar vessel entering the left lobe of the liver had been injected.

The fine featherlike lines extending out from the small end-arteries coming from the main branch show the fineness of the contrast medium. There was no blockage at any point.

The injection of a second artery in the same liver is shown in Fig. 2. This pattern is completely like the first.

The injection of a third artery, shown in Fig. 3, mirrors the first two.

Next, a plastic tube was inserted into the right hepatic artery, 4 cm. from its entrance into the liver. From here the tube was pushed into the liver as far as it would go. The mass was then injected and another roentgenogram was made (Fig. 4). The entire right lobe is outlined in the shadows of the end-arteries. None of the injection mass appears in the left lobe.

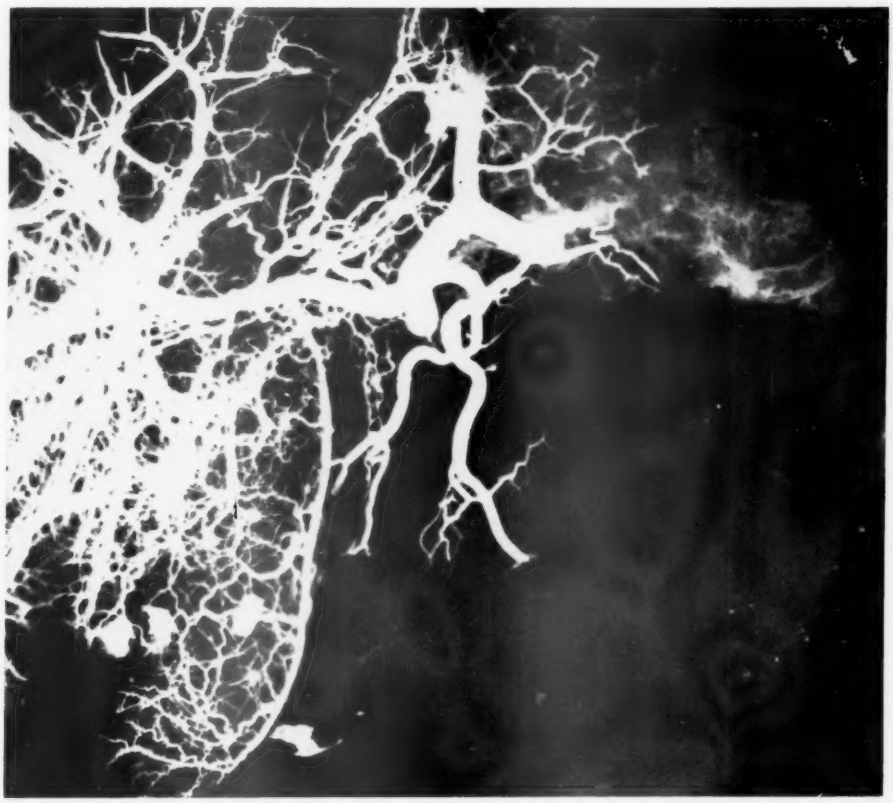

Fig. 6.—The x-ray appearance of a liver injected through the right hepatic artery in the gastrohepatic omentum near, but not at, the hilus. The arterial pattern in the region of the porta is outlined. This also shows the circulation of the gall bladder.

A further injection made into a small branch of the left hepatic artery likewise shows end-arteries only (Fig. 5). There are no connections with the right lobe; there are no anastomoses within the left lobe.

The results of injection in another human liver are shown in Fig. 6. The plastic cannula was inserted into the right hepatic artery 4 cm. outside of the hilus as before, except that it was not allowed to slip deep into the liver substance. This picture is similar to Martens' demonstration. Careful study of the stereoscopic films did not disclose any anastomotic arcades in the liver or in the capsule. This specimen, obtained early in our study, led to the investigation of the smaller arteries at the hilus. Rich, large anastomoses exist between the right and left hepatic arteries in the gastrohepatic omentum. This fact made our earlier work difficult, for leakage occurred through the openings in some of the anastomotic

branches damaged on removal at autopsy. This is easily seen by the shadow shown in some of the plates.

Fig. 7 also is of a human liver injected through the right hepatic artery by a cannula which was not allowed to enter the liver substance. This and Fig. 6 show clearly the over-all pattern of the arterial supply to the liver, and demonstrate conclusively that the intrahepatic arterial circulation is composed of nonanastomosing end-arteries. Both livers (see Figs. 6 and 7), however, show the rich anastomoses over the surface of the gall bladder.

The reason for the errors in the previous studies can better be appreciated by examination of the anatomy of the capsule of Glisson. A section through an injected liver showing

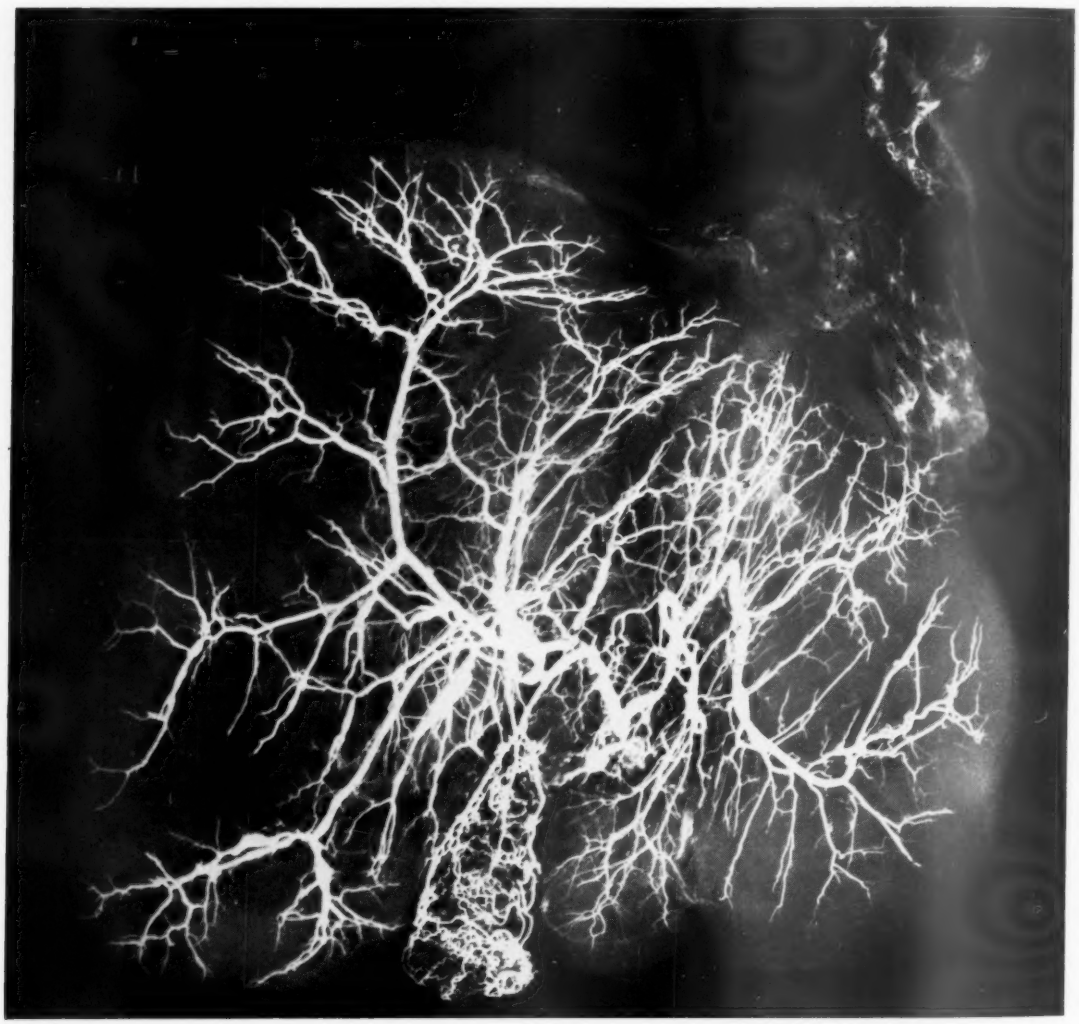

Fig. 7.—Roentgenogram of liver injected through right hepatic artery by a cannula which did not enter the liver substance. This demonstrates the over-all pattern of liver circulation and shows that all arteries are end-arteries with no anastomoses.

the capsule at the hilus is informative (Fig. 8). Here the artery, while seemingly within the liver, is actually lying between two adjacent layers of the intruded capsule. It is in this location in the pedicle, and not in the organ itself, that the division of the artery and the many anastomoses occur.

DISCUSSION

It appears from the injection experiments that Martens had a fault in his technique and therefore erred in his conclusions that there were intrahepatic arterial anastomoses. What he saw were the anastomoses in the gastrohepatic omentum close to the hilus, tucked into the liver with the capsule of Glisson. Our Figs. 6 and 7, which duplicate his and are representative of many similarly injected by us, were studied carefully under the stereoscope. There are no anastomoses in the liver substance. From our work, contrary to Martens' view, no arteries cross the anatomic line of cleavage between the right and left lobes of the liver. Objections by Martens to similar observations by Neuman and Kron on the basis that their mass was too thick, cannot be made of our studies. Study of our original films, and even the prints reproduced in this paper, show the extreme fineness of the injected vessels at the periphery of the secondary lobules. This fine terminal arborization was noted on the liver surface at the time of the injection. It appeared as a delicate red meshwork.

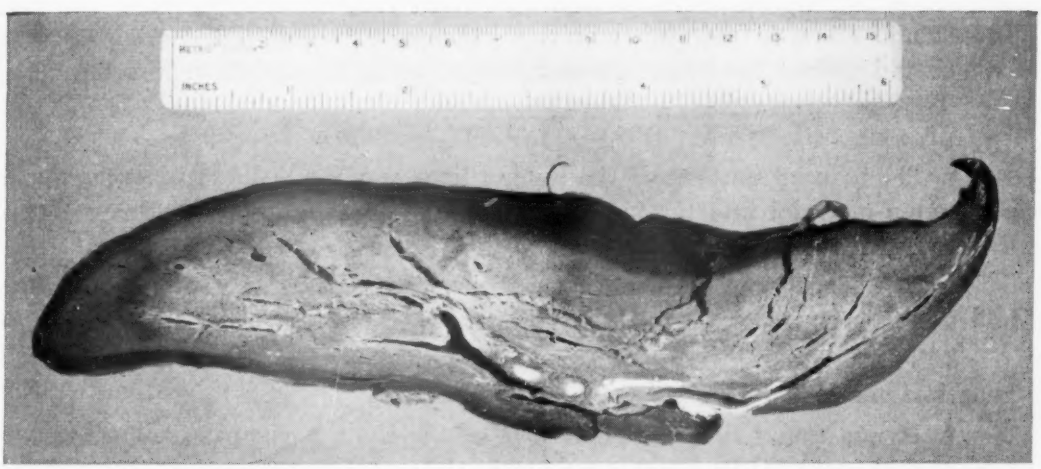

Fig. 8.—Photograph of a section of liver that has been injected. It demonstrates how deeply the capsule of Glisson extends into the liver substance, and how the arteries follow in under its cover.

This presents a new concept of the anatomy of the arterial supply of the liver; the right lobe is composed of secondary lobules, twenty or more, each with an independent arterial blood supply. The clinical importance of this is twofold. First, partial liver resection is anatomically a rational procedure. Second, a wedge of liver with base on the surface might be removed with little danger of embarrassing the circulation in a contiguous part of the organ. If, however, a resection is attempted from the porta outward there is considerable danger of producing massive necrosis of a large wedge of liver tissue.

Ligatures inserted in the under surface of the liver, for example, in the gall bladder bed following cholecystectomy, catching any sizable amount of liver tissue, could easily include an end-artery near its origin, with catastrophic results. The injections confirm the contention of Pickerel and Clay[14] that total

left lobectomy is preferable to partial excision, since total lobectomy is carried out through a line of cleavage devoid of arterial vessels.

It has been taught that liver infarction is rare. The explanation for this is probably found in the fact that the arterial circulation represents only about 20 per cent of the total blood supply brought to that organ. The portal circulation accounts for the rest. From our investigations nonfatal, therefore nondetected, infarcts may be more common than previously thought. These could account for the stormy postoperative course which sometimes follows gall bladder surgery. Since the liver is the most actively regenerating organ in the body, late evidence of such an infarct may not be seen at autopsy. These studies raise the question whether some cases of the hepatorenal syndrome could not be due to accidental occlusion of a relatively large end-artery.

Active bleeding in the neighborhood of the foramen of Winslow may not be due to injury of a large anomalous vessel, but may be due to injury of smaller unnamed anastomotic vessels. These are here shown to be very rich in this area. Their anatomy and relations seen while injecting suggest that bleeding can be controlled safely by finger compression in the foramen of Winslow. This should allow for careful definitive hemostasis rather than mass clamping. This should reduce the concomitant incidence of common duct injuries.

SUMMARY AND CONCLUSIONS

1. The arterial pattern of the human liver was studied by injecting roentgenopaque material into the hepatic arteries and smaller hilar vessels of fresh livers obtained at autopsy.

2. The branches of the hepatic arteries enter the liver substance along with, and under cover of, the capsule of Glisson.

3. There is no intrahepatic communication between the right and left hepatic arteries.

4. It was found that the right lobe of the liver is composed of secondary lobules each supplied by its own end-artery.

5. There are no arterial anastomoses between the smaller arteries of the liver. The vessels are all end-arteries.

6. There is a definite avascular plane between the right and the left lobe.

7. The rich intrahepatic anastomoses between the right and left hepatic arteries previously reported do not exist. They are all extrahepatic and are in the gastrohepatic omentum.

I wish to thank Dr. I. S. Ravdin for providing opportunity and assistance in carrying out these experiments. My appreciation also is extended to Dr. W. E. Ehrich, who furnished most of the fresh anatomic specimens from the autopsy material at the Philadelphia General Hospital. The Department of Pathology of the Hospital of the University of Pennsylvania also supplied some fresh livers from their post-mortem room. To Dr. O. V. Batson I owe the inspiration and guidance without which this work could not have been possible.

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THE EFFECTS OF TEMPORARY OCCLUSION OF THE AFFERENT HEPATIC CIRCULATION IN DOGS

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STATEMENT OF THE PROBLEM

IT HAS been our intent to radically extirpate metastatic hepatic cancer and, since in attempting such excisions large portions of the liver must be removed, adequate hemostasis has been of paramount importance. The lack of adequate hemostatic methods has deterred most surgeons from a direct attack upon hepatic metastasis. To accomplish hemostasis and prevent blood loss, temporary occlusion of the hepatic artery and portal vein has been tried. A perusal of the literature did not reveal how well the liver tolerated this procedure without the development of a fatal necrosis, and so the work to be described has been done to investigate this, as well as factors which might protect the liver undergoing temporary anoxia.

REVIEW OF THE LITERATURE

Temporary occlusion of the hepatic artery and the portal vein was first reported by Duchinova.[9] His aim was to obtain a bloodless field during surgery of the liver, and in order to do this he occluded the vessels at the hepatoduodenal ligament. No effort was made to prevent collateral flow into the liver. In forty-two dogs he performed acute experiments. He performed 176 chronic experiments in nine dogs with intestinal fistulas. Although this method produced a bloodless operative field, Duchinova found that fatalities occurred when the period of occlusion exceeded thirty-five minutes, and that occlusion for one hour was not tolerated by the dogs.

DeWeese and Lewis[7] occluded the afferent hepatic circulation to a segment of liver by permanent ligature of one of the main branches of the portal vein and, simultaneously, temporary occlusion of the artery. This procedure was apparently well tolerated by dogs and the author concluded that maintenance of uninterrupted portal blood flow through a relatively small segment of liver reduced the risk of an occlusion of the afferent hepatic circulation.

Permanent ligation of the hepatic artery was thought to be highly fatal in dogs[1, 5, 13, 14, 26] until Markowitz, Rappaport, and Scott[18-21] reported survival after penicillin administration. Fraser and associates[10] reported a series of thirty-one dogs in which they performed an excision of the hepatic artery. Twenty received antibiotics and eleven served as controls. Whereas the mortality in the controls was 90 per cent, only 35 per cent of the treated group died. Fitts and associates[11] noticed similar beneficial results after Aureomycin administration.

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METHODS

The first aim of our experiments was to find out how long a period of temporary occlusion could be tolerated by a healthy dog. Then a study of the effects of antibiotics on the mortality rate of occlusion was made, and the effect of glucose and adrenocorticotrophin on the survival rate of the preparations was tested. Finally an intermittent type of occlusion was carried out to see if this was less harmful than a continuous one.

Observations were conducted on healthy mongrel dogs weighing from 20 to 30 pounds. During the initial experiments the following determinations were made preoperatively while the dogs were fasting: blood sugar, blood urea nitrogen, serum bilirubin, and alkaline phosphatase.[22] The anesthesia used was either pentobarbital or ether and neither seemed to alter the results.

Under aseptic precautions the abdomen was entered through a midline incision. A specimen of liver was obtained for microscopic examination and then the hepatic artery was isolated and separated from the gastrohepatic ligament. After this the gastroduodenal artery was identified and exposed. The portal vein was then isolated and exposed up to the porta hepatis. Finally, the superior mesenteric artery and celiac axis were isolated, since we found it necessary to occlude these vessels to prevent a hemorrhagic infarction of the intestinal tract. After the dissection was completed, rubber-shod forceps were applied first to the celiac axis and superior mesenteric artery and then, after a one-minute interval, the hepatic artery, just distal to the origin of the gastroduodenal artery, and the portal vein were occluded.

During the first eleven series, in which we were trying to determine the tolerance of dogs to the procedure,[22] the clamps were applied for various time intervals. In Series 10 and 11 the occlusion was performed intermittently allowing a thirty-minute rest interval between periods of occlusion. In Series 16 to 23, the occlusion lasted for one-hour intervals.

Antibiotics were used extensively throughout the various series. Aureomycin was given in doses of 500 mg. by mouth twice daily and 150,000 units of penicillin were given daily in divided doses, morning and afternoon. Premedication with Aureomycin and penicillin was begun forty-eight hours prior to surgery and was continued postoperatively in the survivors.

The systemic blood pressure was recorded in some experiments, and, in an attempt to prevent hypotension, Neo-Synephrine was given intravenously in an infusion of 5 per cent glucose in distilled water.

Adrenocorticotrophin was used as a premedication in Series 18, 19, 20, 21, and 23. Since a study was being conducted concerning the value of ACTH in the treatment of clinical and experimental shock, it was thought advisable to investigate its effect on the shock produced by prolonged liver anoxia. The corticotrophic hormone used was a lyophilized acetone extract of either sheep or hog pituitaries.* Eosinophil counts were performed on the treated as well as on the control animals. The dose of adrenocorticotrophin usually used was 20 mg., given twice a day subcutaneously. When the hormone was used in vehicles other than water, or in different doses, it is so stated in our Tables.

*Supplied by Armour and Company, Chicago, Ill.

In certain cases, serial blood glucose determinations were made. Some preparations were given intravenous 5 per cent glucose infusions postoperatively.

RESULTS

An attempt was made in the first experiments to determine the maximum time of occlusion which could be tolerated by normal dogs which had had no premedication (Table I). Nine dogs had the entire afferent hepatic circulation occluded for a period of thirty minutes or longer, and among these there were only two survivors. One of these tolerated the occlusion for one hour, while the other tolerated it for thirty minutes. The pathologic findings in those that died were characteristic of prolonged anoxia of the hepatic parenchyma and the severity of the morphologic changes seen were related to the time interval between surgery and death in these dogs. The two animals which survived showed no changes and were in good health when they were sacrificed. Histologic examination of their livers showed a normal architecture.

TABLE I. OCCLUSION OF ENTIRE AFFERENT FLOW TO THE LIVER

SERIES NUMBER	NUMBER OF DOGS	DURATION OF OCCLUSION	RESULTS	
			DIED	SURVIVED
1.	4	60 minutes	3	1
2.	1	45 minutes	1	-
3.	4	30 minutes	3	1
4.	4	25 minutes	1	3
5.	4	20 minutes	-	4
6.	4	15 minutes	-	4
7.	3	60 minutes*	3	-
8.	4	30 minutes*	1	3
9.	3	30 minutes—penicillin only	3	-

*Received: Aureomycin, 10 mg. per pound of body weight twice daily; penicillin, 150,000 units twice daily; Ringer's solution, 15 c.c. per pound daily.

When the period of anoxia was less than thirty minutes (Series 4, 5, 6) the dogs tolerated the procedure well. Though one of four died in the series subjected to twenty-five minutes of afferent vascular occlusion, none among those dogs occluded for twenty minutes or less died.

Series 7, 8, and 9 (Table I) comprise dogs that received antibiotics before and after occlusion of the hepatic circulation for various periods of time. In Series 7 the occlusion lasted sixty minutes, while in Series 8 and 9 the time interval was thirty minutes. Aureomycin and penicillin were administered to the dogs in Series 7 and 8, while penicillin alone was used in Series 9. When the period of circulatory arrest lasted one hour no survivors were obtained in spite of antibiotics. This was well borne out in later experiments (Table IV, Series 16, 17, 22). Though they were ineffective when the occlusion period was one hour, administration of both Aureomycin and penicillin improved the survival rate after an occlusion period of thirty minutes, for among four dogs in this series only one died while six of the seven dogs which had no medication or penicillin alone failed to survive.

In view of the fact that the liver could not well tolerate a prolonged period of anoxia, it was decided to arrest the circulation in an intermittent fashion in the hope that allowing a period of recovery from anoxia would permit a longer

total vascular occlusion. In these experiments the forceps were applied for fifteen minutes, then released for thirty minutes, and finally reapplied for a second period of fifteen minutes, resulting in a total occlusion period of thirty minutes. Antibiotics were given to one group of dogs and withheld from the other.

Table II shows the results when this method was employed. An intermittent occlusion of the afferent hepatic circulation, for a total occlusion period of thirty minutes, was less harmful than a continuous one. Of nine dogs, without medication, subjected to intermittent occlusion only three died within forty-eight hours, while six of seven dogs undergoing continuous occlusion and receiving no medication or penicillin alone died (Series 3 and 9). Among nine additional dogs receiving both Aureomycin and penicillin and submitted to intermittent occlusion (Series 11), only one died and this one had no histologic liver changes. This evidence also supports the effectiveness of combined antibiotic therapy in reducing the mortality of liver anoxia.

TABLE II. INTERMITTENT* OCCLUSION OF ENTIRE AFFERENT FLOW TO THE LIVER

SERIES NUMBER	NUMBER OF DOGS	PROCEDURE	RESULTS	
			DEATH	SURVIVED
10.	9	15 on—30 off—15 on	3	6
11.	9	15 on—30 off—15 on†	1	8

*The afferent vascular flow was occluded for 15 minutes, released for 30 minutes, and clamps were reapplied for 15 minutes.

†Aureomycin, penicillin, and Ringer's solution were administered.

Occlusion of the hepatic artery alone for one hour was without ill effects in three dogs as shown in Table III (Series 12).

TABLE III. OCCLUSION OF EITHER THE PORTAL VEIN AND SUPERIOR MESENTERIC ARTERY OR HEPATIC ARTERY ONLY

SERIES NUMBER	NUMBER OF DOGS	PROCEDURE	TREATMENT	DIED	SURVIVED
12.	3	1 hour, hepatic artery	None	-	3
13.	4	1 hour, portal vein and superior mesenteric artery	None	3	1
14.	4	1 hour, portal vein and superior mesenteric artery	Heparin (2 c.c.)	2	2
15.	4	1 hour, portal vein and superior mesenteric artery	Aureomycin and penicillin	1	3

Table III (Series 13, 14, 15) comprises three groups of dogs which had occlusion of the superior mesenteric artery and portal vein for one hour without occlusion of the hepatic artery. Whereas three out of four dogs survived when penicillin and Aureomycin were administered, without antibiotics three out of four died.

The 111 experiments on an equal number of dogs which comprise Table IV were designed to evaluate the effectiveness of adrenocorticotrophin. The experiments on controls and treated dogs were conducted simultaneously, and

the decision as to which animals received adrenocorticotrophin was made by a chance selection. All animals had an afferent hepatic circulatory occlusion for one hour. Of thirty-nine control animals which did not receive adrenocorticotrophin, none survived (Series 16 and 22). This in spite of the fact that all received Aureomycin and penicillin. Thirty-six dogs received ACTH which had been prepared from hog pituitaries, and of these nineteen dogs died and seventeen survived. All these dogs received antibiotics and, as was the case in every instance when the drugs were administered, treatment began forty-eight hours prior to operation. Eosinophil counts were made and will be discussed elsewhere.

TABLE IV. OCCLUSION OF THE ENTIRE AFFERENT HEPATIC CIRCULATION FOR ONE HOUR

SERIES NUMBER	NUMBER OF DOGS	AUREOMYCIN	PENICILLIN	DIED	SURVIVED	ADDITIONAL THERAPY
16.	27	500 mg. daily	100,000 units	27	0	None
17.	4	500 mg. daily	100,000 units	4	0	Neo-Synephrine, 10 mg. intravenously in glucose
18.	24	500 mg. daily	100,000 units	13	11	ACTH (pork) 20 mg. twice daily
19.	12	500 mg. daily	100,000 units	6	6	ACTH (pork) 20 mg. twice daily in gelatin
20.	12	500 mg. daily	100,000 units	10	2	ACTH (sheep) 20 mg. twice daily
21.	12	500 mg. daily	100,000 units	10	2	ACTH (sheep) 30 mg. twice daily, glucose 66 Gm. twice daily by stomach tube
22.	12	500 mg. daily	100,000 units	12	0	Glucose 66 Gm. twice daily by stomach tube
23.	8	None	None	6	2	ACTH (pork) 20 mg. twice daily and intravenously

Twenty-four dogs received adrenocorticotrophin which had been extracted from sheep pituitaries. Twenty died and only four survived. Glucose in doses of 66 Gm. was given twice daily by stomach tube to twelve of these dogs as well as to the twelve control animals mentioned above. No beneficial effect was noted from glucose administration in either group (Table IV, Series 21 and 22).

Eight dogs had no antibiotics but were given ACTH (pork) for forty-eight hours prior to surgery, and an intravenous infusion of 5 per cent glucose containing 20 mg. of ACTH during the operation. Two dogs survived while six died (Series 23). Hence, this procedure was of some benefit as compared to the control series.

To prevent the hypotension that occurred during occlusion of the afferent hepatic circulation, four dogs, previously premedicated with the usual dosage of antibiotics, were given an intravenous infusion of 5 per cent glucose and 10 mg. of Neo-Synephrine. This was administered by slow drip, but none of these dogs survived the procedure (Series 17).

Eosinophil Count.—The eosinophil count was determined in control dogs as well as in dogs treated with ACTH, according to the method described by

TABLE V. VARIATION IN EOSINOPHIL COUNTS

	NUMBER OF DETERMINATIONS	NO CHANGE OR INCREASE FROM INITIAL COUNT	DECREASE OF LESS THAN 50 PER CENT OF INITIAL COUNT	DECREASE OF 50 PER CENT OR MORE OF INITIAL COUNT	SURVIVORS
Control	14	3	2	9	None
ACTH treated	31	6	7	18	8
Survivors alone	8	1	3	4	8

Thorne.[24] Determinations on fourteen control dogs and thirty-one treated dogs were performed and the results are shown in Table V.

Of the fourteen control animals, three showed no change or a rise in eosinophils four hours after the initial determination; two had a decrease of less than 50 per cent of the initial value and in nine a decrease of 50 per cent or more of the initial determination was observed. In the ACTH group, where thirty-one determinations were made, no change or a rise in count was observed in six instances. In seven dogs a decrease of less than 50 per cent below the initial count was observed; eighteen dogs showed a decrease of 50 per cent or more in eosinophil count.

There was no correlation between changes in the eosinophil count and survival rate but the analysis of the data showed the following:

1. None of the control dogs survived regardless of their eosinophil response.
2. Of the thirty-one ACTH treated dogs in whom eosinophil counts were made a total of eight survived.
    a. Of the six that showed either no change or an increase in the eosinophil count, one survived.
    b. Of those showing a decrease of less than 50 per cent, three of seven survived.
    c. Four of eighteen survived of those showing a decrease of 50 per cent or more of the initial eosinophil count.

TABLE VI. BLOOD SUGARS (IN MILLIGRAMS PER 100 C.C. OF BLOOD)

DOG NUMBER	FASTING	30 MINUTES OF OCCLUSION	END OF SURGERY	ONE HOUR AFTER SURGERY	TWO HOURS AFTER SURGERY	THREE HOURS AFTER SURGERY
1.	100	65	68	57	53	died
2.	90	74	47	53	died	
3.	82	77	65	74	died	
4.	65	65	63	60	52	died
5.	93	100	97	177	185	147 died

Blood Sugar Levels.—Determination of blood glucose levels was made early in our series because our first thought was that the dogs were dying from hypoglycemia as occurs in the case of hepatectomized dogs.[17] Although there is usually a drop in blood sugar at the completion of the operation, the administration of large amounts of glucose did not help the dogs. It neither prolonged their lives nor produced any improvements in their condition. Five examples are tabulated in which serial blood sugar levels were determined (Table VI).

Blood Pressure and Circulatory Effects.—Recording of the systemic blood pressure was made in several experiments. There was invariably a drop in the blood pressure accompanied by extreme pallor of the mucous membranes and associated with clinical signs of shock whether ACTH was administered or not. When recovery from the anesthetic began, the dogs usually had large bloody bowel movements. No attempt at replacement of lost blood was made; administration of a vasopressor drug was of no benefit in preventing the shock.

DISCUSSION

Although Duchinova[9] stated that the afferent hepatic circulation of a dog could be occluded for thirty-five minutes, we failed to corroborate his findings since an occlusion of over twenty minutes in our experiments produced fatalities. The difference may be due to the fact that we endeavored to occlude the hepatic artery distal to the origin of the gastroduodenal artery to prevent collateral flow while he did not. In our experiments the flow of blood through collaterals was further impeded by occlusion of the celiac axis and the superior mesenteric artery.

Aureomycin and penicillin, when given to the preparations, reduced the mortality which follows a thirty-minute occlusion period. This is probably due to their action on the bacterial flora of the dog's liver.[8, 10-12, 15, 19-21] Beyond thirty minutes of occlusion the high fatality rate was unchanged by the administration of antibiotics.

Intermittent occlusion of the afferent flow was tried in eighteen dogs and this resulted in the survival of fourteen. This procedure yielded a higher number of survivals than a continuous occlusion for the same time interval. It is believed that one of the reasons for this finding is that the growth of anaerobes, which is stimulated by oxygen lack in the hepatic tissues, was inhibited by the re-establishment of circulation. Since the period of anoxia before reoxygenation was relatively short, slight or no damage to the liver was produced. Another possibility is that an opportunity was given the anoxic liver to replenish its stores of glycogen and nutrients while the noxious metabolites were swept away from the cells by the circulation. Finally, a lesser production of the vasodilator material described by Shorr,[23] when occlusion is intermittent, may account for the lowered mortality. Shorr has demonstrated the presence in the circulation of a vasodilatory material (V.D.M.), which is manufactured by the anoxic liver during hypovolemic shock. In liver slices incubated in either serum or in Kreb's bicarbonate medium, in an atmosphere of 95 per cent nitrogen and 5 per cent carbon dioxide, no V.D.M. was produced for twenty to thirty minutes. However, from then on it was produced in increasing quantities. At the same time anaerobiosis prevented the normal destruction of this substance in the liver, so it may be that in our work interruption of the anoxic period prevented the liver from reaching the stage of anoxia when large amounts of V.D.M. could be produced and yet not be destroyed. Whether this mechanism exerted an influence in our experiments is difficult to assess but the possibility is worth while considering.

ACTH was administered to five series of dogs which can be divided into three groups. Those receiving pork ACTH and antibiotics comprised thirty-six dogs and yielded seventeen survivors. When ACTH (sheep) and antibiotics were administered, four out of twenty-four survived. These results are highly significant when compared to the survival rate among the fifty control dogs (Series 1, 7, 16, 22); despite a similar period of occlusion, there was only one survivor.

The explanation for the species difference demonstrated by pork and sheep pituitary extracts is not immediately apparent. Cluxton[6] has stated that "some differences have been noticed by other investigators in small laboratory animals."

As to the protection afforded by pork ACTH, it is possible that it is exerted through the action of the adrenal on carbohydrate metabolism. Stimulation of the adrenal cortex by adrenocorticotrophin produces a large amount of physiologically active steroids with an oxygen atom or hydroxy-radical at the 11 carbon position. These substances are powerful stimulants to glyconeogenesis and the end result of their effect is a great increase in glycogen deposition in the liver.[2-4, 16, 25] Adrenal cortical hormones also produce an increase in the level of circulating glucose as shown by Long and Katzin.[16] If this were the only mechanism involved in the beneficial effect of ACTH, the results should be duplicable by the administration of large doses of carbohydrates. To test this idea, glucose in doses of 66 Gm. twice daily were fed by stomach tube to twelve control and twelve ACTH (sheep) treated dogs. The regular kennel diet was given and glucose water (20 per cent) was the only drinking fluid allowed. Yet the results showed no beneficial effect gained over other comparable groups.

Whereas dogs that received ACTH (pork) and antibiotics have a good survival rate (seventeen out of thirty-six), the exclusion of antibiotics from the treatment plan decreased the survival rate to two out of eight. The reduction of the normal liver flora produced by antibiotics could be responsible for this difference.

A great drop in systemic blood pressure was noticed in all our experiments and it was of similar magnitude regardless of the medication administered. Probably the most important reason for the development of shock is the sequestration of blood in the gastrointestinal vascular bed. Although the intestines became pale soon after the arterial blood supply was occluded, at the end of the procedure the color was a dark purple. This congestion of the intestines was doubtless due to an accumulation of blood brought through the collateral circulation. Damage to the intestinal wall and to the intestinal vasculature must have taken place. This was substantiated by the fact that most of our preparations had large bloody bowel movements upon recovery from anesthesia. This mechanism alone could explain the production of shock, but the influence exerted by an increased V.D.M. production should also be considered and was not ruled out by our observations. Efforts to maintain blood pressure by the use of Neo-Synephrine were unsuccessful in four experiments. Whether a

different drug or blood replacement would be useful is a matter under consideration, and it needs further exploration.

The eosinophil count, as a measure of adrenal activity, was highly unsatisfactory in our hands. This is not surprising since all of the animals used were new to our kennel and were not adjusted to the environmental change. Administration of antibiotics to controls as well as treated dogs can also account for a reduction in the circulating eosinophils.

SUMMARY AND CONCLUSIONS

1. In dogs, twenty minutes was the maximal period of continuous occlusion of the hepatic artery and portal vein tolerated without evidence of hepatic necrosis.

2. Aureomycin and penicillin were of benefit in preventing death during a thirty-minute period of occlusion. This effect may be due to a reduction in the number of anaerobic organisms normally present in canine liver.

3. Intermittent occlusion carried out by allowing a thirty-minute rest between two fifteen-minute occlusion periods reduced the mortality rate below that of continuous occlusion. Only three of nine dogs died after such a procedure while six of seven died from a continuous occlusion for thirty minutes.

4. Occlusion of the entire afferent vascular flow to the liver for one hour was fatal in forty-nine dogs of fifty. Of these, forty-six had received generous doses of Aureomycin and penicillin, but still none survived.

5. ACTH in combination with antibiotics decreased the mortality due to occlusion of the afferent hepatic circulation for one hour. Pork ACTH was decidedly better, in our experience, than the hormone extracted from sheep pituitaries.

6. Large amounts of glucose fed orally did not alter the results when given to control or ACTH (sheep) treated dogs.

7. A state of shock with marked hypotension resulted from occlusion of the entire afferent hepatic flow and it did not respond to Neo-Synephrine intravenously.

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THE ANTRAL PHASE OF GASTRIC SECRETION BEFORE AND AFTER VAGOTOMY—EXPERIMENTS ON GASTRIC POUCH DOGS

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THE antral phase of gastric secretion may be defined as the secretory response of the stomach to stimuli acting on the antral mucosa. That the mechanism in this phase is humoral, rather than nervous, has been well established.[10, 16, 19, 24] The antrum plays a definite and significant role in gastric secretion, and is probably unique in its capacity to secrete gastrin.[8, 9, 12, 38] Experimental results which have seemed to contradict these statements can usually be explained by failure to measure quantity as well as acidity of secretion, disregard of the anatomy of the antrum, use of inadequate stimuli, or preparation of water-soluble instead of protein-like extracts of antral mucosa.

Numerous clinical and experimental observations have linked antral function with the occurrence of peptic ulcer. General conclusions from this work may be summarized as follows:

1. Antral exclusion, whether with simple gastroenterostomy or gastric resection, increases the incidence of jejunal ulcer in patients operated on for peptic ulcer.[1, 13, 14, 17, 28, 33, 40]

2. In animals, antral exclusion with gastroenterostomy, or transplantation of the antrum into the intestine (Koennecke, 1922; Dragstedt, 1951) is followed by a much higher percentage of stomal ulcers than is simple gastroenterostomy, but protection is afforded by a subtotal gastrectomy.[4, 5, 18, 21, 32, 41]

3. In animals, and probably in man, gastric secretion is increased by antral exclusion, and decreased by antral resection.[11, 15, 35, 41]

4. The main factor in the greater incidence of ulcer after antral exclusion is, in all probability, an increase in gastric secretion resulting from stimulation of the antral mucosa by regurgitated duodenal contents,[20, 36] together with a lack of the normal inhibitory effect of acid[31, 34, 36] in the antrum and upper duodenum.

It is well known that gastric motor and secretory functions are distinctly altered after complete division of the vagi, but the particular effect of this operation on the antral phase of acid secretion has been little studied. Orbeli (1907) measured the secretory response of Pavlov pouches to test meals (introduced via gastrostomy), and then converted the pouches to the Heidenhain type, thus removing vagal innervation. The gastric phase was largely conserved, but there was a marked decrease in volume of pouch secretion after test meals, a decrease in pepsin, and a decrease in acidity in some instances.

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Lim, Ivy, and McCarthy (1925) state that vagotomy had no effect on the secretory response to distention of the stomach in dogs. Meyer and associates (1948) noted lowered secretory response to caffeine given by tube in vagotomized ulcer patients. Significant, quantitative data have not been reported on this question, and the present investigation attempts to provide such data.

METHODS

The normal stomach or single gastric pouches are unsatisfactory for study of the gastric phase, because anything put into the pouch, except perhaps a distending balloon, contaminates the secretion.

Employing mongrel dogs of medium or large size, an innervated total gastric pouch and an esophagoduodenostomy were prepared. Then the stomach was divided into separate parts by cutting the wall beneath the plexus of nerves, which mainly fan out from the lesser curvature. Innervation was proved by means of the insulin test, and by a remarkable change in response to all types of stimuli after transthoracic vagotomy. Since antral pouches secreted little or no acid, functional innervation of these could not be proved. Fig. 1 diagrams pouches in eleven of the dogs studied. Subcutaneous transplanted pouches were made in several of the dogs. Vagotomy was performed transthoracically, in the course of study of Dogs 1, 3, and 5.

At the time an experiment was to begin, rubber balloons were attached to the catheters draining the pouches. The balloons were then emptied into test tubes at thirty-minute intervals. After three control specimens had been obtained, the stimulus was given, and eight more thirty-minute specimens were collected.

Specimens were measured and analyzed by colorimetric titration for free and total acid, using Töpfer's reagent and phenolphthalein as indicators. Pepsin activity was determined by the method of Anson and Mirsky,[2] which employs hemoglobin as the substrate.

Histamine was injected subcutaneously in the form of Histamine Acid Phosphate, in a dose of 0.5 mg. of the base. The dose of pilocarpine nitrate was 3 mg., given subcutaneously. Insulin was given intravenously, 0.67 u. per kilogram of body weight; blood sugar was determined before injection, and at three half-hour intervals after injection. The test was not accepted unless the blood sugar went below 50 mg. per cent.

Gastric phase stimuli were prepared in the amount of 50 c.c. of liquid and placed in a 100 c.c. syringe, which was then connected directly to the catheter in the pouch to be stimulated. The pouch was flushed with the stimulant by repeatedly injecting and withdrawing amounts not greater than 5 c.c., for thirty minutes. The specimen from the stimulated pouch was thus mixed with the stimulant during this period, and was not analyzed. The corresponding specimens from other pouches were analyzed.

Meat extract was prepared by dissolving 12.5 Gm. of Armour's Beef Extract in 50 c.c. of water. The alcohol solution used was 7 per cent ethanol in water. Pancreatic juice was obtained from dogs with isolated duodenal pouches, from which bile was excluded.

Distention was produced by means of rubber balloons, introduced into the pouches and filled with a measured volume of water. The effective stimulating volume for each pouch was determined by finding the amount which produced

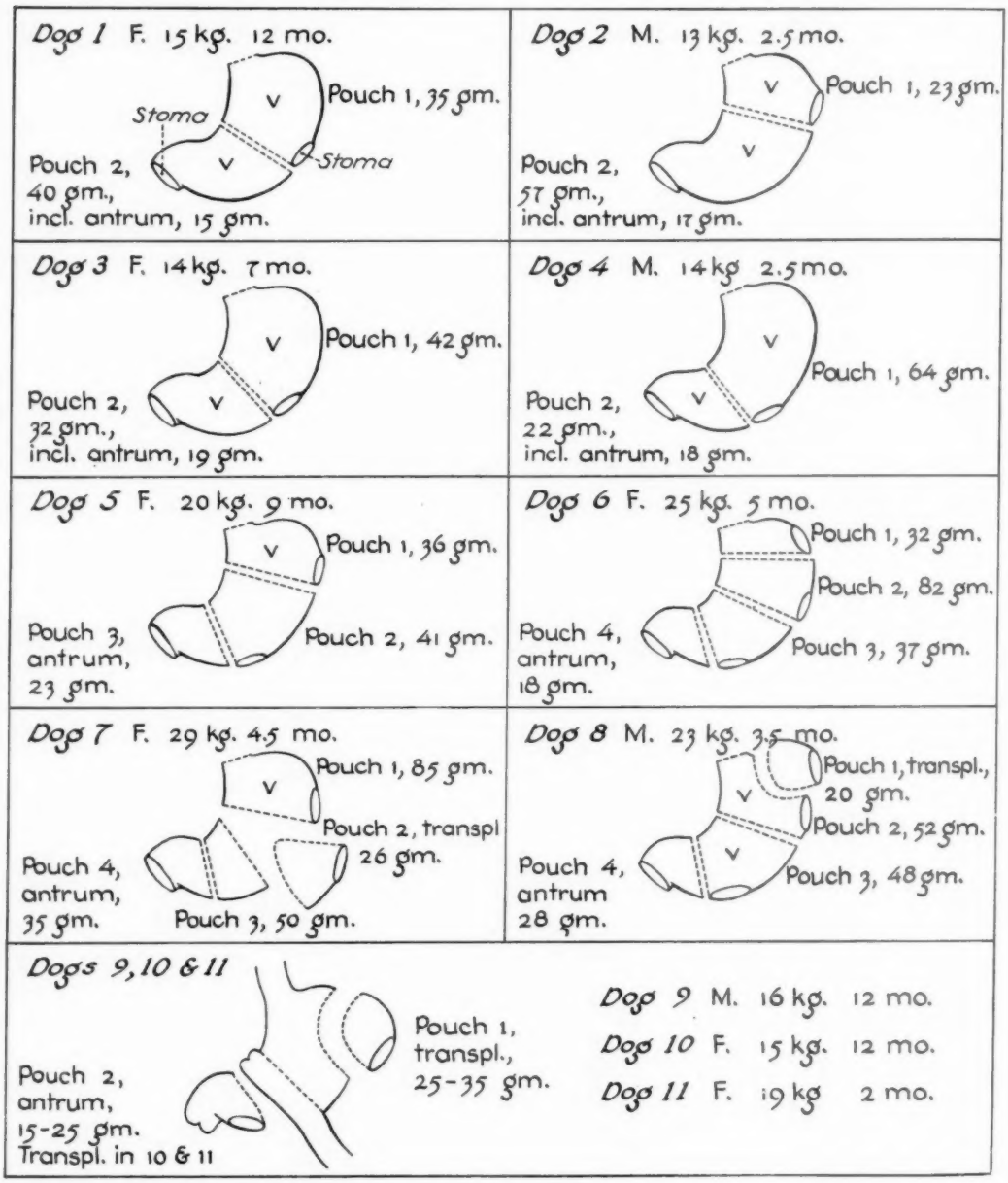
Dog 1 F. 15 kg. 12 mo.
Stoma
V
Pouch 1, 35 gm.
Pouch 2, 40 gm., incl. antrum, 15 gm.
Stoma
Dog 2 M. 13 kg. 2.5 mo.
Pouch 1, 23 gm.
Pouch 2, 57 gm., incl. antrum, 17 gm.
Dog 3 F. 14 kg. 7 mo.
Pouch 1, 42 gm.
Pouch 2, 32 gm., incl. antrum, 19 gm.
Dog 4 M. 14 kg 2.5 mo.
Pouch 1, 64 gm.
Pouch 2, 22 gm., incl. antrum, 18 gm.
Dog 5 F. 20 kg. 9 mo.
Pouch 1, 36 gm.
Pouch 2, 41 gm.
Pouch 3, antrum, 23 gm.
Dog 6 F. 25 kg. 5 mo.
Pouch 1, 32 gm.
Pouch 2, 82 gm.
Pouch 3, 37 gm.
Pouch 4, antrum, 18 gm.
Dog 7 F. 29 kg. 4.5 mo.
Pouch 1, 85 gm.
Pouch 2, transpl 26 gm.
Pouch 3, 50 gm.
Pouch 4, antrum, 35 gm.
Dog 8 M. 23 kg. 3.5 mo.
Pouch 1, transpl., 20 gm.
Pouch 2, 52 gm.
Pouch 3, 48 gm.
Pouch 4, antrum 28 gm.
Dogs 9, 10 & 11
Pouch 1, transpl., 25-35 gm.
Pouch 2, antrum, 15-25 gm.
Transpl. in 10 & 11
Dog 9 M. 16 kg. 12 mo.
Dog 10 F. 15 kg. 12 mo.
Dog 11 F. 19 kg 2 mo.

Fig. 1.—Diagrams of gastric pouches. Sex, weight at operation, and length of experimental period after operation are listed. Pouch weights were obtained post mortem. Pouches having proved vagal innervation are labeled with a V.

evidence of discomfort (extreme restlessness or retching) and reducing this amount by 10 per cent.

In recording data, the degrees of free acidity, or milliequivalents of free HCl per liter, have been multiplied by the volume (in liters) of each thirty-

minute specimen to give the milliequivalents of free HCl secreted in this unit of time. Pepsin units per unit volume were also multiplied by the volume of the specimen, and are given as pepsin units secreted per unit of time.

RESULTS

1. *The Receptive Area for the Second Phase of Gastric Secretion.*—Antral stimulation was invariably followed by increased gastric secretion, unless the resting secretion happened to be very high, as may occur in innervated pouches. Usually the response was very clear-cut (Table I).

TABLE I. SUMMARY OF TWO HUNDRED FORTY EXPERIMENTS IN ELEVEN MULTIPLE-POUCH DOGS, IN WHICH A SINGLE POUCH WAS STIMULATED BY THE VARIOUS MEANS INDICATED

	POUCH STIMULATED							
	ANTRUM				CORPUS OR FUNDUS			
STIMULUS	NUMBER OF EXPERIMENTS	NUMBER OF POSITIVE RESPONSES	PER CENT POSITIVE RESPONSES	P*	NUMBER OF EXPERIMENTS	NUMBER OF POSITIVE RESPONSES	PER CENT POSITIVE RESPONSES	P*
1. Meat extract	71	59	83	<.01	68	19	28	0.11
2. Distention	27	20	77	<.01	15	4	27	0.23
3. Water	13	8	61	<.01	12	3	25	0.26
4. Alcohol	11	10	91	<.01	8	5	63	0.03
5. Pancreatic juice	7	6	86	<.01	8	2	25	0.32
Total	129	103	80		111	33	30	

*Probability that the result given would have occurred by chance (see text).

Stimulation of other parts of the stomach was not followed by a consistent response except when alcohol was used. While there occasionally appeared to be a response to fundic stimulation in single experiments, the average values in a series invariably leveled out. The exception in the case of alcohol may be due to the fact that it is absorbed from the stomach, unlike most other materials, and is an effective gastric stimulant when given intravenously. If a stimulus was effective, the highest value for free acid occurred in period 4, 5, or 6, and this was called a positive response. Table I shows that stimulation of the corpus or fundus of the stomach by various means did not increase the frequency of a positive response, as just defined, above that expected when no stimulus was given, except when alcohol was used.*

Antral stimulation was followed by a significant response in each group of experiments.

2. *The Relative Quantity of Antral Phase Secretion.*—The data, shown in Table II, indicate that meat extract applied to the antrum for thirty minutes produces on the average a secretory response about equal to that following subcutaneous injection of pilocarpine (3 mg.), and over one-half that produced by injection of 0.5 mg. of histamine base.

*The probability of the observed result occurring by chance was calculated from the general form of the expansion of the binomial: $\frac{n!}{(n-r)!\,r!}\,p^{n-r}\,q^{r}$, where n is the number of experiments and r is the number showing no response[37]; p was given the theoretical value, 3/11 or .27, and q, .73. Actual values in thirty-six experiments (in which no stimulus was given) were .25 and .75.

TABLE II. AVERAGE SECRETION OF FREE HCl BEFORE AND AFTER VAGOTOMY, IN FUNDIC POUCHES DURING A PERIOD OF NINETY MINUTES AFTER STIMULATION, IN DOGS 1, 3, AND 5

	BEFORE VAGOTOMY			AFTER VAGOTOMY			
STIMULUS	NUMBER OF EXPERIMENTS	MEQ. HCl PER 90 MINUTES	STANDARD ERROR	NUMBER OF EXPERIMENTS	MEQ. HCl PER 90 MINUTES	STANDARD ERROR	PER CENT DECREASE
1. None	27	1.62	0.23	25	0.03	0.01	98
2. Histamine	17	5.79	0.78	17	1.85	0.26	68
3. Pilocarpine	15	2.90	0.50	14	1.24	0.19	58
4. Meat extract in antrum	18	2.99	0.51	17	1.15	0.17	62
5. Insulin	8	1.13	—	3	0.04	—	96
6. Distention of antrum	6*	1.34	—	6*	0.30	—	78
7. Water in antrum	5†	1.99	—	5†	0.06	—	97
8. Alcohol in antrum	3†	1.42	—	6†	0.67	—	52
9. Average, all experiments	99	2.74	—	93	0.81	—	70

*Two dogs.
†One dog.

3. *The Effect of Vagotomy on the Antral Phase.*—The gastric secretory response of Dogs 1, 3, and 5 to various stimuli was studied before and after thoracic vagotomy. After the nerves were divided, there was an immediate and striking decrease in resting secretion and in response to all stimuli, as indicated in Table II. The decrease in response to meat extract in the antrum after vagotomy was about 60 per cent. The dogs gained weight and improved in general condition after vagotomy, the change being apparent within a week. Hence the change in secretion could not have been the result of a deterioration in the dogs' health.

An alternative interpretation of these data may be considered, namely that vagotomy merely eliminates the high resting or basal secretion of the innervated stomach pouch, and that the secretory response itself is unaffected. (Lim, 1924; Code, 1951.) The hypothesis was tested by subtracting the average secretion of the pouches for ninety minutes before stimulation from the figures given in Table II, where the acid secretion is given for ninety minutes after stimulation, before and after vagotomy. These data were supplemented with results obtained in three other dogs (12, 13, and 14) with single innervated total gastric pouches, before and after vagotomy, on stimulation with histamine. A definite decrease in response to stimuli was still apparent after vagotomy when basal secretion was subtracted in each case. The decrease averaged 59 per cent, as compared to 70 per cent (Table II) when basal secretion was not subtracted.

4. *The Relation of Pepsin Secretion to the Antral Phase.*—Uvnäs (1948) has suggested that there is a humoral phase of pepsin secretion.

In the experiments recorded in Table III, three injections of 0.5 mg. of histamine base were given subcutaneously to multiple pouch dogs at two-hour intervals. Twelve half-hour specimens were collected from each pouch. Acidity was invariably high, except in antral pouches. After the first two hours, in some of the experiments an intragastric stimulus was administered along with the second dose of histamine. Specimens from each two-hour period following injection of histamine were pooled, separately for each pouch, and analyzed for pepsin.

TABLE III. AVERAGE PEPSIN SECRETION BEFORE AND AFTER VAGOTOMY, FROM POUCHES OF THE CORPUS AND FUNDUS IN DOGS 1, 3, AND 5; REPEATED HISTAMINE STIMULATION, WITH OTHER STIMULI GIVEN AT THE BEGINNING OF THE SECOND PERIOD*

	PREVAGOTOMY				POSTVAGOTOMY			
ADDITIONAL STIMULUS	NUMBER OF EXPERIMENTS	PEPSIN UNITS × 10^{-3} 1	2	3	NUMBER OF EXPERIMENTS	PEPSIN UNITS × 10^{-3} 1	2	3
1. None	9	239	277	269	9	62	35	60
2. Meat extract, antrum	9	255	579	475	9	171	174	141
3. Meat extract, corpus	9	300	412	274	9	153	84	79
4. Pilocarpine					9	135	349	274

*Values given are for three successive two-hour collection periods, averaged from three experiments of each type on each dog.

When an additional gastric phase stimulus was applied either to the antrum, or (before vagotomy) to the other parts of the stomach, there was inconclusive evidence of slight stimulation of pepsin secretion, as shown in Table III.

It is evident that pepsin secretion was decreased after vagotomy, but that pilocarpine was still an effective stimulus. The other differences are of doubtful significance.

Another variation of the experiment described was carried out in dogs 7 and 8, which had four pouches each. A steady intravenous infusion of saline, 120 c.c. per hour, was given, containing 0.42 μg per kilogram per minute of histamine base. After one and one-half hours, during which accumulated pepsin was presumably washed out by the copious acid secretion, collection was begun from each of the four pouches. Specimens were obtained hourly for five hours; after the first collection, an intragastric stimulus was applied in one of the pouches. Acidity and volume of secretion were constantly high in all except antral pouches. The hourly specimens were analyzed for pepsin.

The results, given in Table IV, indicate a gradual, incomplete, washing-out of pepsin by histamine-induced secretion alone, with occasionally some increase in the enzyme when intragastric stimuli were added. The differences are of doubtful significance, because of the wide variations in control values, even in the subcutaneous pouches. The feeding of meat in Dog 7 was followed by an increase of pepsin secretion in the innervated pouch much larger than any found after intragastric stimuli.

It may be concluded that the gastric phase of pepsin secretion, under the conditions of these experiments, probably exists, but is of minor importance.

DISCUSSION

The question arises as to whether the effect of vagotomy on the antral phase is due to an alteration in antral function or to an effect primarily on the responsiveness of the parietal cells. Depression of response to all known stimuli, including injected gastrin,* after vagotomy suggests that the latter is the case.

*Unpublished experiments.

TABLE IV. AVERAGE SECRETION OF PEPSIN IN DOGS 7 AND 8 DURING CONTINUOUS INTRAVENOUS INJECTION OF HISTAMINE*

ADDITIONAL STIMULUS	NUMBER OF EXPERIMENTS	POUCH NUMBER	PEPSIN, UNITS PER HOUR × 10-3				
			1	2	3	4	5
Dog 7							
1. None	4	1	445	649	403	288	150
		2	29	44	43	34	22
		3	99	262	309	300	181
		4			(No free acid)		
2. Meat extract, antrum	3	1	309	109	98	101	145
		2	18	18	14	14	16
		3	257	271	179	249	140
3. Meat extract, corpus	4	1	125	132	132	217	276
		2	18	23	23	28	25
		3	103	108	94	93	183
4. Distention of antrum	4	1	361	353	334	295	264
		2	51	51	56	47	49
		3	183	316	367	430	403
5. Distention of corpus	4	1	752	427	210	272	210
		2	18	27	19	16	15
		3	87	92	148	274	133
6. Ingested meat	1	1	440	1102	730	615	319
		2	18	18	14	14	16
		3	196	245	311	258	187
Dog 8							
1. None	5	1	5	6	6	7	6
		2	1674	1123	945	965	620
		3	324	365	333	364	234
		4	8	10	10	15	10
2. Meat extract, antrum	3	1	3	4	5	5	12
		2	940	840	1033	1617	1213
		3	251	303	384	653	460
3. Meat extract, corpus	2	1	6	7	10	14	10
		2	1021	717	574	873	979
		3	266	328	284	402	272
		4	9	15	13	26	28
4. Distention of antrum	1	1	2	1	3	5	6
		2	1020	717	1336	1556	1254
		3	256	299	391	512	321
		4	12	10	2	14	11
5. Distention of corpus	2	1	6	4	6	6	11
		2	863	614	528	942	1113
		3	374	383	394	526	342
			8	11	22	9	13

*Hourly collections were begun after ninety minutes; additional stimuli were given after the first hour sample was collected.

Some alteration of antral function, of course, cannot be ruled out in these experiments.

The action of pilocarpine and histamine was studied mainly for comparison with the antral phase. The cephalic phase, as obtained by feeding the dog or tempting with food while collecting pouch juice, would have been a more interesting comparison, but the secretion so obtained was very erratic, and often scanty. A direct comparison of the first and second phase in the same animals could not be made fairly, because the appetites, eating habits, and conditioned reflexes to feeding in the total pouch dogs were distinctly altered from the normal.

Pancreatic juice was tested in connection with the role of regurgitation of duodenal contents into the antrum in causing gastric secretion, especially after antral exclusion. Pancreatic juice was a considerably more potent stimulant than water, in Dog 1, but was less effective than meat extract in Dogs 1 and 5.

Kim and Ivy (1936), using single pouches, found little or no response to perfusion with pancreatic juice. A small response could have been masked by the perfusion fluid.

A great deal of effort was directed toward the study of pepsin secretion in response to gastric phase stimuli. The results are inconclusive. It may be that different stimuli, e.g., fish extract instead of meat extract (Babkin, 1935), would have produced a positive response. Nevertheless, vagal impulses are probably much more important than humoral effects in increasing the output of pepsin. The unstimulated output of pepsin during repeated injections of histamine was decreased by somewhat over 50 per cent after vagotomy (Table III).

SUMMARY AND CONCLUSIONS

1. A series of 240 experiments in eleven dogs with multiple gastric pouches has shown that the gastric phase of gastric secretion depends almost entirely on stimulation of the antral mucosa.

2. The gastric secretory response to meat extract kept in the antrum of dogs for thirty minutes is about one-half as much as that produced by 0.5 mg. histamine base injected subcutaneously.

3. In three dogs with multiple innervated gastric pouches, transthoracic vagotomy decreased the antral phase secretion by about 60 per cent. The response to histamine was decreased 68 per cent, and that to pilocarpine 52 per cent, in the same animals. Unstimulated resting secretion was decreased 98 per cent, although the dogs were in better physical condition after vagotomy.

4. The secretion of pepsin, measured in multiple pouch dogs during continuous histamine stimulation, was possibly slightly increased by stimulation of the gastric mucosa, particularly the antrum. Cephalic phase stimuli, and pilocarpine, were much more effective under the same conditions. Pepsin output was decreased by over 50 per cent after vagotomy. The gastric humoral phase of pepsin secretion is probably of little importance.

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REMOVAL OF THE XYPHOID PROCESS AS AN AID IN OPERATIONS ON THE UPPER ABDOMEN

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IN CERTAIN operations, which include such procedures as total gastrectomy, esophagogastrostomy, subdiaphragmatic vagotomy, splenectomy, and diaphragmatic herniorrhaphy, one of the principal aims of the surgeon must be to obtain as good an exposure as possible of the left subdiaphragmatic region if these operations are to be carried out with a minimum of trouble and a maximum of efficiency. Every surgeon with the experience of these procedures knows how inadequate exposure of this region may militate against their satisfactory performance since such an exposure may render even the insertion of a deep suture a matter of the greatest difficulty while the repeated efforts which may be necessary on occasion to clamp successfully a deeply seated severed artery not only add to the surgeon's tribulations but may also result in a worrying deterioration of the patient's condition.

With such thoughts in mind one of us (J. H. S.), in a recent article on total gastrectomy,[3] discussed various incisions in relation to their adequacy of exposure of this region and expressed the opinion that the best exposure was that afforded by the thoracoabdominal incision. It was pointed out, however, that postoperative pulmonary complications constitute a definite risk entailed by the use of this incision. While acknowledging the excellence of the exposure this incision provides, we cannot but feel that, in general, one which would obviate the necessity of opening the pleural cavity is to be preferred, granted that at the same time it gives an exposure good enough to be considered satisfactory, even though perhaps falling somewhat short of that which can be achieved through the thoracoabdominal incision. One of the incisions discussed was the upper midline, the simplest of all, rather to point out its limitations than to extol any virtues it might possess, although the writer mentioned that he had not tried the additional removal of the xyphoid process as advocated and practiced by Lefevre.[2] Since the writing of this article we have taken the opportunity to carry out this procedure on a number of occasions with results so favorable as to prompt this brief communication.

It is of interest that Lefevre himself, in his discussion on total gastrectomy, devotes only a small paragraph to a consideration of the removal of the xyphoid process, yet, after indicating that one of the conditions essential to the satisfactory performance of this operation is an approach which will permit ease of maneuverability, he makes the arresting statement that the key to the problem which such an approach presents lies in the resection of this process, pointing out that it results in an astonishing enlargement of the operative

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field. The only other reference we have noted in the literature to removal of this process is that by Finsterer,[1] who also dismisses the procedure briefly by merely mentioning that in performing total gastrectomy he always removes the xyphoid process as suggested by Lefevre.

Lefevre himself, however, makes no mention of what soon appeared to us to follow removal of the xyphoid as a natural sequence, namely, the upward extension of the peritoneal incision which removal of this process permits. This further simple procedure is of considerable importance as it results in even greater enlargement of the operative field. To those who are unfamiliar with these simple modifications of the upper midline incision we would point out that by them this routine incision, of itself often leaving much to be desired as a means of access to the abdominal cavity, is readily converted into one which, in the majority of cases requiring the types of operation mentioned previously, will provide the adequate exposure so necessary for their satisfactory performance.

SURGICAL ANATOMY

No great knowledge of anatomy is necessary in undertaking the removal of the xyphoid process, as this small structure has merely to be separated from its soft tissue attachments to allow its piecemeal excision by rongeur forceps. Moreover, the simplicity of the procedure is enhanced by the facts that in the vicinity concerned there are no important structures likely to be damaged and that such hemorrhage as occurs is only of minor degree and consequently readily controlled. A brief account is given here of the principal anatomic relationships of the xyphoid process as confirmed by a recent small series of dissections upon cadavers and observations made at operations. The linea alba in most instances passes upward anteriorly over the lower edge of the xyphoid to gain attachment to the upper one-half or one-third of its anterior surface, although on some occasions it will be found attached to this edge as well as to the whole of the anterior surface of this process. The fibers of the linea alba decussate with those of the anterior costoxyphoid ligament, this ligament forming a well-defined structure extending from the sternal end of the seventh costal cartilage across the chondroxyphisternal junction to the anterior surface of the xyphoid, in contradistinction to its posterior counterpart which is so small that it is frequently difficult to delineate. Attached to its posterior surface are the lowest, and almost horizontal, fibers of the transversus thoracis muscle and, most pertinent to the present discussion, the sternal origin of the diaphragm. This origin consists of two fleshy muscular slips separated from each other by a narrow linear interval containing areolar tissue, while each is separated laterally from the costal origin by a small triangular gap which is also filled with loose areolar tissue and through which the superior epigastric branch of the internal mammary artery descends into the abdominal wall. Detachment of this sternal origin from the posterior surface of the xyphoid severs the front mainstay of the domed diaphragm, releasing (and thus relaxing) this portion of the muscle and allowing it to fall backward, carrying with it the peritoneum covering it.

If the xyphoid is now removed, one then looks down upon the upper surface of the anterior portion of the diaphragm through which the incision can then be extended upward.

TECHNIQUE AND RESULTS

The abdomen is opened through a routine upper midline incision extending from the tip of the xyphoid cartilage to the umbilicus and, after examination of the abdominal viscera, the decision is made regarding the type of operation to be performed. While it is realized that many upper abdominal procedures can be carried out satisfactorily through this incision, yet, if that which is contemplated is one demanding access to the left subdiaphragmatic region, it will be noted that the xyphoid and the tense portion of the diaphragm attached to it form an overhanging and unyielding canopy which renders this access both awkward and difficult, and in such a case we consider that any surgeon would be well advised to avail himself of the help he will obtain from removal of the xyphoid, a procedure which can be done in only a few minutes. The incision is extended upward through the skin and superficial fascia to a point about 2 cm. above the xyphisternal junction, the linea alba is incised up to its insertion, and the lower and lateral margins and anterior and posterior surfaces of the cartilage are separated from their attachments by sharp dissection, the cartilage itself then being excised with rongeur forceps and being hemorrhage controlled. It will be found now that the edges of the abdominal wound can be retracted further outward to an appreciable extent because of release of the costal margin due to severance of the attachments of the costoxiphoid ligament, transversus thoracis muscle, and sternal origin of the diaphragm. However, the full advantage of having removed the xyphoid lies in the fact that it is now possible to increase further the size of the wound by incising the diaphragm and its peritoneal lining upward toward the dome of this muscle for a distance of no less than 4 or 5 cm. The increase in exposure thus brought about is nothing short of astonishing. The edges of the incision can now be retracted one-half again as much as was previously possible (Fig. 1, *b* and *d*), thereby greatly enlarging the size of the operative field. Two further important features, which we have endeavored to illustrate diagrammatically (Fig. 2), resulting from the incision having been enlarged in this manner, are at once discernible. In the first place, the level of the upper end of the incision is now such that it almost reaches that of the dome of the diaphragm, resulting in a much more direct, and therefore easier, approach to the structures attached to the inferior surface of this muscle or lying in contiguity with it, such as the left lobe of the liver and its triangular ligament, the spleen, the esophageal hiatus and abdominal portion of the esophagus, and the cardiac portion of the stomach. Second, the upper edges of the incised diaphragm and peritoneum now lie in a plane much posterior to that in which they lay when held forward by their attachments to the xyphoid so that for practical purposes the wound assumes a shallower conformation with the result that these subdiaphragmatic structures noticeably become more accessible for manipulations. The combined effect of these advantages accruing from

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removal of the xyphoid and the further upward extension of the peritoneal opening made possible by this procedure may be summarized as resulting in improvement of the operative conditions to a degree that enables the surgeon to carry out necessary procedures with a dispatch and ease in turn reflected in decreased operating time, more accurate technique, and the avoidance of shock

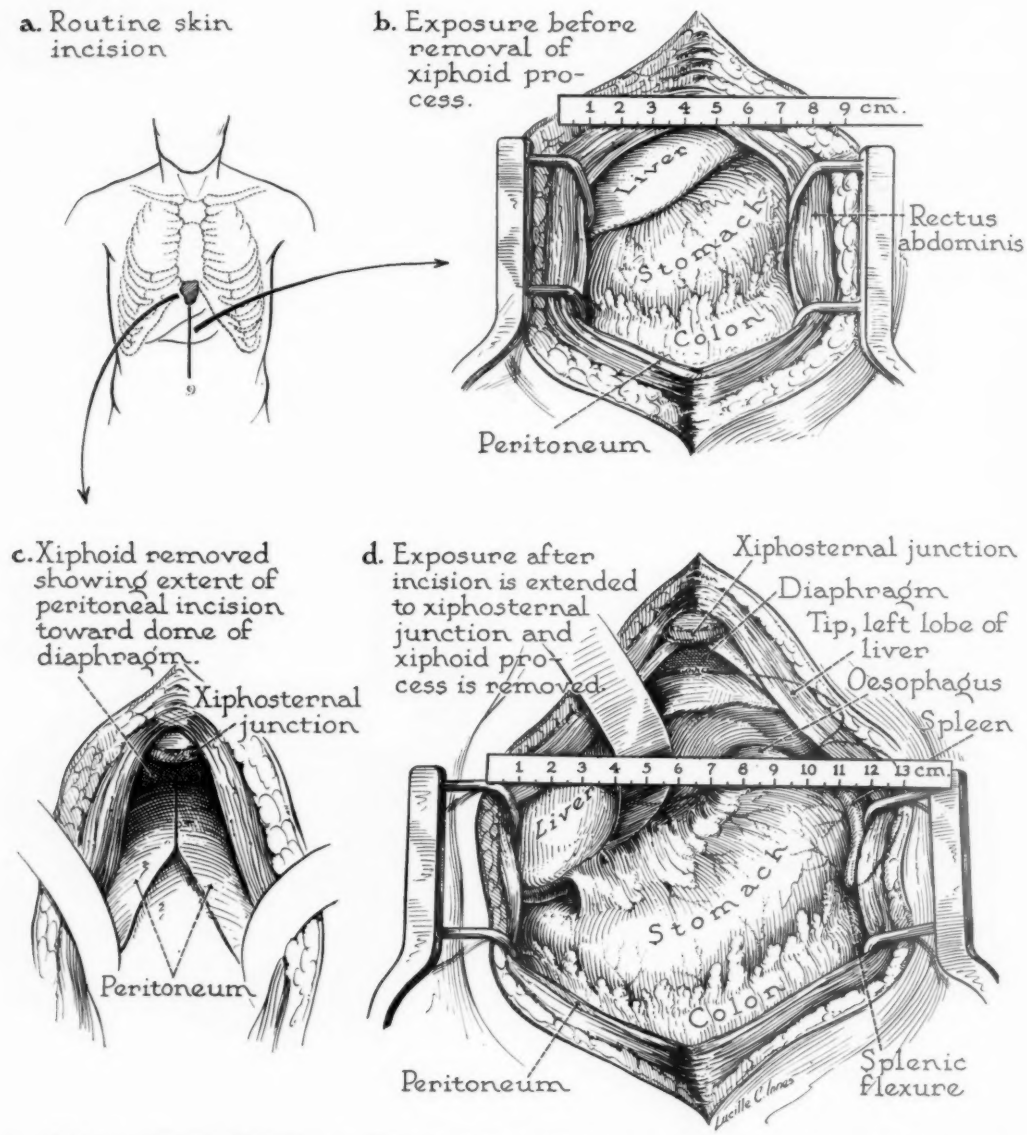

Fig. 1.—Upper abdominal midline incision; enlargement of the operative field resulting from the removal of the xyphoid process and the upward extension of the peritoneal opening made possible by this procedure. (From photographs taken at operation.)

or its reduction to a minimum. We consider that no surgeon can fail to be both impressed and gratified at finding himself the recipient of so many operative benefits in return for so little expenditure in time and effort. As a result of our experience we find ourselves in complete agreement with the opinion

expressed by Lefevre that the key to the problem of adequate access to the left subdiaphragmatic region lies in the excision of the xyphoid process.

Closure of this incision is the same as that of the original incision except for the upper end. After the peritoneal opening has been closed, a bite of the diaphragm is taken with each of three or four sutures used to appose the edges of the linea alba in this situation. Tying of these sutures then effectively obliterates the dead space which would otherwise exist due to the removal of the xyphoid. Insertion of these particular sutures presents no difficulty nor is the time taken to close the incision added to appreciably.

During the hospital postoperative period of none of those patients in whom the procedure had been carried out was there noted any additional discomfort such as could have been attributed to the removal of the xyphoid, and patients seen as long as a year after their operation did not have any complaints referable to this region.

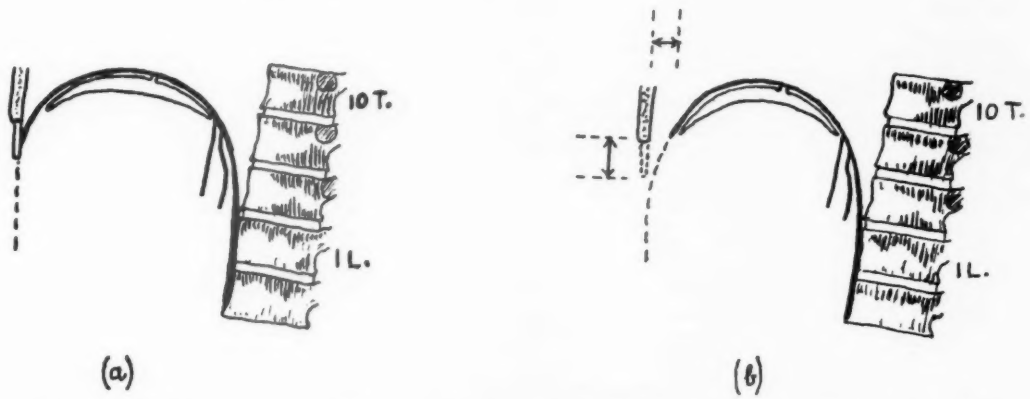

Fig. 2.—Diagrams in sagittal plane showing upper midline incision before, *a*, and after, *b*, removal of the xyphoid process. Note in *b* the upward extension of the peritoneal incision and the resultant decrease in anteroposterior depth of the wound.

It is conceivable that in a small percentage of cases the configuration of the patient may be such that the advantages gained by removal of the xyphoid and the upward extension of the peritoneal opening may still leave the surgeon dissatisfied with the adequacy of the exposure. We would point out, therefore, that in such instances either the incision still can be converted into a thoracoabdominal one or it can form the starting point of upward splitting of the lower end of the sternum (median sternotomy) to allow further retraction as advocated by Wangensteen.[4] However, it is worth bearing in mind that these procedures are in themselves of no small moment and are likely to add considerably to the length of the operation, whereas removal of the xyphoid is not only a simple procedure easily and quickly performed, but also one which obviates the necessity of having to close a complex incision at the end of what may have proved to be a long and tedious operation.

SUMMARY

Removal of the xyphoid process and the further upward extension of the peritoneal opening made possible by this procedure are simple expedients

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whereby the routine upper abdominal midline incision is rendered adequate for most surgery of the upper abdomen, for they effect an astonishing enlargement of the operative field, resulting in easy accessibility in such operations as total, or high partial, gastrectomy, esophagogastrostomy, subdiaphragmatic vagotomy, diaphragmatic herniorrhaphy, and splenectomy, and eliminating the need, in most cases, of complex incisions such as those of the thoracoabdominal or median sternotomy types.

Patients tolerate well the performance of these simple modifications of the upper abdominal midline incision, and no disturbing aftereffects have been noted either during the immediate postoperative period or at a later date.

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FURTHER STUDIES ON THE ROLE OF BACTERIA IN DEATH FROM ACUTE PANCREATITIS IN DOGS

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SINCE oral Aureomycin reduces the mortality rate of experimental hemorrhagic pancreatitis in dogs from 90 per cent to nearly zero,[1] the pancreatitis per se is not fatal and death must be attributed to the superimposed infection. Data showing an increased incidence of positive clostridial cultures suggested that a clostridial infection was involved in the fatal outcome, especially since polyvalent gas gangrene antitoxin appeared to exert a favorable effect on the survival rate.[1] In this report further data are given showing that while clostridia certainly are involved, death frequently must be attributed to other pathogens.

The operative procedure for producing uniformly fatal hemorrhagic pancreatitis, by injecting 10 c.c. of sterile dog bile into the pancreatic duct, has been described.[1]

Different types of treatment were tried, as follows:

Group I.—Ten dogs were actively immunized with polyvalent clostridial toxoid.*†[2] Ten to twenty-one days following the last dose, hemorrhagic pancreatitis was produced. Six dogs survived. These were sacrificed three to twelve days after inducing the pancreatitis. All showed active or resolving pancreatitis. The survival rate is equal to that obtained with clostridial antitoxin.[1]

Comment: These data implicate clostridia in the lethal outcome. But the distinct superiority of oral Aureomycin suggests that other bacteria may also be involved, either independently or synergistically with the clostridia.

Group II.—(A) Two grams of neomycin twice daily was given to a group of ten dogs until coliform bacilli were absent from the feces. This required treatment from two to five days. Hemorrhagic pancreatitis was then produced. (B) In another group of ten dogs, 6 Gm. of neomycin in 150 c.c. of saline was given by gavage, immediately before producing pancreatitis. Three grams of neomycin was given orally eight hours after operation, and twice daily for the next two days to survivors.

Five dogs survived in each group. In both groups average survival time of the nonsurvivors was fifty-three hours, in contrast to the average survival time of twenty hours in untreated dogs.

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*One ml. of the toxoid was given subcutaneously, to be repeated three and six weeks subsequently.

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Comment: This result is distinctly inferior to that obtained with oral Aureomycin. Since neomycin does not affect clostridia, a 50 per cent survival rate must signify that clostridia cannot be the exclusive pathogens involved in the fatal outcome. Whether the effectiveness of either antibiotic is due to its action upon the flora within the intestine or within the tissues (pancreas) or both is not certain. Oral neomycin is relatively nonabsorbable, but since 3 per cent can be absorbed, it may exert an antibacterial effect on the tissues. Data relative to this question were obtained in the next group of experimental animals.

Group III.—Ten animals were pretreated with 200 mg. of polymyxin B daily by mouth for three to five days until the stools were free of coliform organisms. The last dose was given four hours before pancreatitis was produced. The survival rate was 40 per cent. Since polymyxin affects only gram-negative organisms and since it is not absorbed from the intestine in any detectable quantity we are obliged to implicate these organisms to a considerable though not predominant degree in the lethal outcome. These data reaffirm our view that intestinal bacteria, invading the peritoneal cavity in response to the chemical inflammation induced by the hemorrhagic pancreatitis, are involved in the fatal outcome.[1] But the evidence does not permit a conclusion as to the relative roles played by these bacteria and those already present in the tissues of the abdominal cavity.

Group IV.—Since neomycin is effective against gram-negative organisms, and to a lesser degree against gram-positive cocci, but not against clostridia, it was anticipated that giving polyvalent clostridial antitoxin (Lederle) and neomycin might achieve an additive effect, whether clostridia and gram-negative bacilli act synergistically or independently.

Accordingly, ten dogs were given 4 Gm. of neomycin daily for three to five days and 10 c.c. of polyvalent antitoxin subcutaneously for three days prior to the induction of pancreatitis.

Five of the ten dogs survived. This was an unexpectedly poor result. The superiority of oral Aureomycin may be due to a more potent action on Clostridia than the antitoxin can exert, or, because it is better absorbed than neomycin, to a greater effect on nonclostridial organisms in the tissues.

Group V.—Because of data to the effect that Aureomycin may act by some mechanism not related to its antibacterial properties, 5 Gm. of inactivated Aureomycin was given daily for six days by mouth to each of a group of five dogs. (Inactivation was induced by keeping a 5 per cent saline solution of the drug at 37° C. for four days. The powder obtained by drying the solution for forty-eight hours at 37° C. showed a 10,000 fold reduction in antibacterial potency when tested with a twofold dilution method.)

There were no survivors in this group, nor was the survival time prolonged. As a control for this group five dogs were treated likewise with the active drug. Of these, four survived. It is clear that only the antibacterial properties of Aureomycin are involved in the cure.

Bacteriologic examination was made at post mortem on forty surviving dogs sacrificed between the third and thirty-first day after operation, and on twenty-

nine nonsurviving animals, immediately after death. The incidence of positive clostridial cultures in the liver, peritoneal fluid, and pancreas was very high, definitely more so than in specimens taken at the operation.[1] No qualitative cultural differences were observed between surviving and nonsurviving dogs (Table I). Gram-negative bacilli were found in less than 5 per cent of the organs examined and only in small numbers.

TABLE I. BACTERIOLOGIC FINDINGS FROM CULTURES TAKEN AT AUTOPSY FROM SURVIVORS AND NONSURVIVORS

	PERITONEUM		LIVER		PANCREAS	
Nonsurvivors (29)						
Clostridia	22	79%	26	97%	24	86%
Small number of Coli or Pseudomonas together with Clostridia	1		2		1	
Sterile cultures	6		1		4	
Survivors (40)						
Clostridia	33	85%	36	97%	34	87%
Small number of Coli or Pseudomonas together with Clostridia	1		3		1	
Sterile cultures	6		1		5	

The protective action of antibiotics does not consist of an elimination of the bacteria, but of a suppression of their pathogenic potential.

It appears that virulence and toxin production of bacteria in the dog's tissues are suppressed until activated by tissue injury, in this case created by the release of chemically irritating pancreatic enzymes by the cytolytic action of the injected bile.

SUMMARY AND CONCLUSIONS

Clostridia are a significant factor in death from acute experimental pancreatitis in the dog but other bacteria appear to be involved, either synergistically or independently. Since a nonabsorbable antibiotic, such as polymyxin, exerts a considerable beneficial effect, there is support for the conclusion reached in a previous communication that intestinal bacteria invade the peritoneal cavity in response to the chemical irritation from pancreatic enzymes. The greater effectiveness of Aureomycin may be due in part to its broader range of action within the intestine. Since the favorable effect of clostridial toxoid signifies an action upon clostridia within tissues, the superiority of Aureomycin is probably due to its absorbable fraction acting upon clostridia already in the tissues.

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PERFUSION OF THE PULMONARY CIRCULATION BY NONPULSATILE FLOW

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THIS communication describes a method of obtaining a nonpulsatile flow of blood for the perfusion of an entire, intact circulation, and presents the data obtained during by-pass of the right side of the heart with nonpulsatile perfusion of the pulmonary circulation in dogs for periods of three hours. The results to be reported represent a portion of a larger project concerned with the development of an extracorporeal heart pump mechanism and of techniques of by-pass of blood around the heart or heart and lungs. Interest in this problem of nonpulsatile perfusion was aroused in the course of pump development, for the question of whether a pump should emit a pulsatile or nonpulsatile flow involves basic pump design. It was therefore decided to conduct a limited number of experiments to determine the importance of the pulse in maintenance of the lesser circulation and of the greater circulation. This paper deals mainly with the former.

EXPERIMENTAL METHOD

The right heart is by-passed by diverting blood from the right atrium into an extracorporeal heart pump mechanism. The pump mechanism emits a pulsatile flow which is rendered nonpulsatile by means of a depulsating apparatus whose outflow is channeled into the left pulmonary artery of the experimental animal. Since the cannula in the left pulmonary artery is a T tube, blood is returned to both lungs for oxygenation. During the perfusion the main pulmonary artery is completely occluded, ensuring that the depulsator outflow is the only source of blood for perfusion of the lesser circuit (see Fig. 1).

The pump mechanism is essentially an air piston pump with a rubber membrane interface. The piston chamber contains an upright cylinder for the direct calibration of the stroke volume. The rate can be counted, and thus the minute volume flow can be easily computed. The pump mechanism has been described previously.[1, 2]

The depulsator is an artificial peripheral resistance apparatus consisting of a membrane surrounded by a large quantity of air. The membrane is

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stretched within a discarded pump chamber. The air between the membrane and the pump chamber wall is in communication with 1,500 c.c. of air in a bottle. By means of a three-way stopcock and mercury manometer, enough air is inserted into the bottle to surround the membrane with a pressure of the order of the systolic pressure of the circulation to be artificially maintained (40 mm. Hg for the pulmonary circulation and 160 mm. Hg for the systemic circulation in dogs). The resultant outflow from the depulsator is nonpulsatile at a pressure of 5 mm. Hg when the pulmonary circulation is perfused and

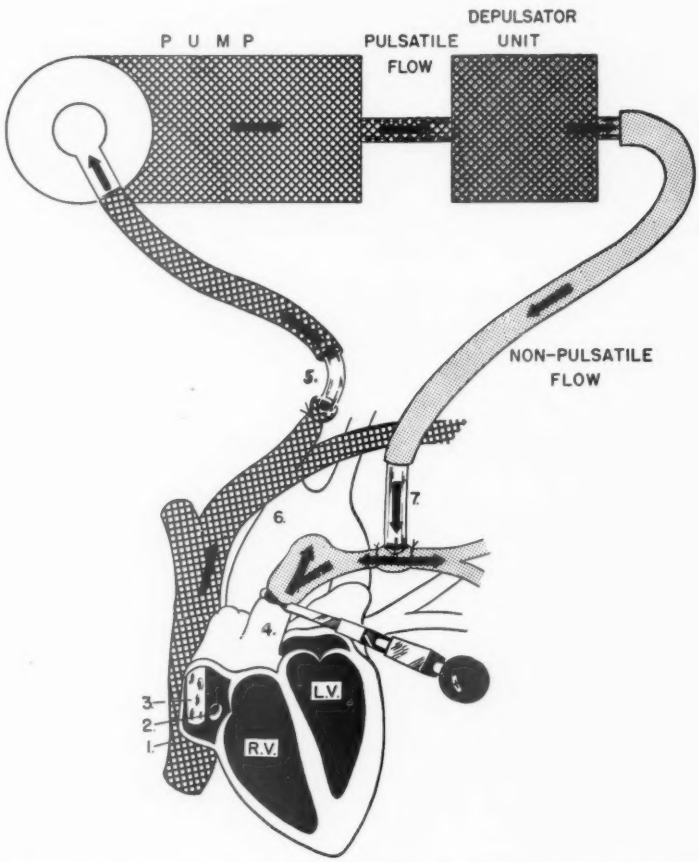

Fig. 1.—Diagram of blood circuit during nonpulsatile perfusion of the pulmonary circulation. (1) Inferior vena cava, (2) Coronary sinus opening in right atrium, (3) Tip of "venous" cannula within right atrium, (4) Main pulmonary artery occluded by Blalock clamp, (5) "Venous" cannula inserted through left external jugular vein, (6) Aorta, (7) T cannula in place in left pulmonary artery. Arrows depict the direction of blood flow.

120 mm. Hg when the systemic circulation is perfused. This depulsator is adequate for acute experiments, but is not recommended for experiments in which the animal is expected to recover because of marked destruction of platelets. The technical details of cannulation of the experimental animal have been published elsewhere.[2] Heparin is administered only to the blood donor dogs (2 mg. per pound intravenously).

The nonpulsatile perfusion of the pulmonary circulation is maintained for three hours. During the perfusion, the left heart continues its function of

maintenance of the systemic circulation while the right heart, which is now by-passed, decreases in size and becomes nonfunctioning although it continues to beat. At the end of the three-hour perfusion period the main pulmonary artery occlusion is released and the pump is stopped. The cannula is removed from the left external jugular vein which is ligated on both sides of the cannulation site. The cannula is removed from the left pulmonary artery and the cannulation defect is repaired using 000000 arterial silk. The animal is given enough protamine sulfate intravenously to reduce the clotting time to normal. The amount of protamine sulfate necessary varies from 50 to 100 mg. The neck and chest incisions are then closed in layers using silk. The cannulae are removed from the femoral vessels and the animal is returned to his cage.

The control experiments consisted of a group of twenty-four experiments in which the intact pulmonic circulation was perfused using a *pulsatile* flow. In one of the controls the perfusion was carried on for three hours. In twenty-three of the controls the pulsatile perfusion of the pulmonary circulation was carried on for a period of from one to two hours. A series of five consecutive test experiments were conducted using the method outlined above. The pulmonary circulation in these experiments was perfused for three hours using a *nonpulsatile* flow. The fact that a nonpulsatile flow had been attained in the pulmonic circuit is demonstrated by the electromanometric tracings in Fig. 2.

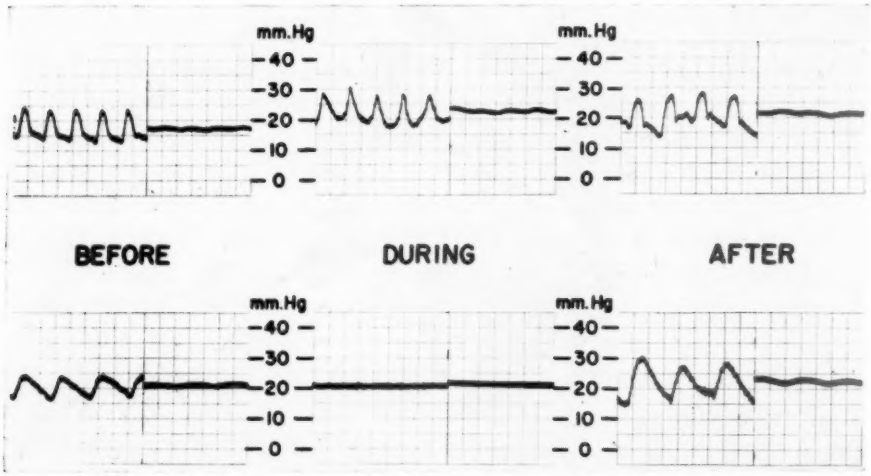

Fig. 2.—Electromanometric pulse-wave traces taken from within the main pulmonary artery. Each trace is accompanied by a strip of electronically integrated mean pressure record. The "DURING" traces were recorded at the end of a three-hour period of perfusion of the lesser circuit. The top row of traces was recorded during a control experiment using a pulsatile flow; the bottom row was recorded during a nonpulsatile perfusion experiment. Note the complete absence of pulse waves during the nonpulsatile perfusion.

CONTROL EXPERIMENTS USING A PULSATILE PERFUSION OF THE PULMONARY CIRCULATION

In the single three-hour control experiment the by-pass procedure was uneventful. The animal's color remained pink and the state of his reflexes stable throughout the entire procedure. The systemic blood pressure was adequately maintained at all times. The pulse wave tracings from within the main pulmo-

nary artery (distal to the occlusion) demonstrated that during perfusion the systolic, diastolic, pulse, and mean pressures were nearly identical with those respective pressures both before and after the perfusion (see Fig. 2). At the end of the three-hour *pulsatile* perfusion, analysis of arterial whole blood revealed the following representative values: oxygen content, 20.8 volumes per cent; oxygen saturation, 93 per cent; carbon dioxide content, 36.1 volumes per cent. From these figures it can be seen that these lungs functioned adequately during the perfusion. This animal received 1,700 c.c. of blood in transfusions during the procedure. The estimated blood loss during this eleven-hour procedure was 1,500 c.c. The hematocrit value was forty-eight at the beginning of the procedure, forty-nine at the end of the procedure, and forty-nine on the first postoperative day several hours after a meal of water, milk, and raw meat. The lungs showed no untoward signs at any time. The animal recovered and regained his normal preoperative behavior. This dog died of empyema on the twelfth postoperative day. Necropsy revealed that the lungs were grossly and microscopically normal except for moderate compression atelectasis resulting from pressure by the empyema fluid.

Similarly, in six further control experiments the right heart alone was by-passed. The pulmonary circulation was artificially perfused using a pulsatile flow for shorter periods of from one to two hours. All animals exhibited good color, adequate blood pressure, and normal reflexes throughout the procedure. Five of these control animals recovered from the procedure with no evidence of lung damage referable to the perfusion clinically or at post-mortem examination. The sixth animal died of a technical error.

The remaining seventeen control experiments have been previously reported.[2] During these experiments both sides of the heart were by-passed and the animal's own lungs were used as the means of oxygenation. Five of these animals died as a result of technical errors. During the twelve successful experiments the pulmonary (and systemic) circulation was perfused for one to two hours using a pulsatile flow. The animals exhibited good color and normal arterial oxygen saturation with normal or lowered carbon dioxide content of arterial blood during the perfusion. Twelve animals recovered from the procedure and showed no clinical or post-mortem evidence of lung pathology relative to the perfusion.

TEXT EXPERIMENTS USING A NONPULSATILE PERFUSION OF THE PULMONARY CIRCULATION

Five consecutive experiments were all successfully completed. Three of these animals died of hemothorax during the first day after operation probably as a result of platelet deficiency. Two animals recovered; one subsequently died of empyema on the twelfth postoperative day, and the other survived four months at which time he was sacrificed for examination. All five experiments are considered valid for evaluation of the functional effect of nonpulsatile flows.

During the three-hour *nonpulsatile* perfusion, the pump output remained stable in all experiments. Pump output correlated well with that in the control experiments. During perfusion the animals remained in good condition: The

color of the mucous membranes remained pink, the corneal and respiratory reflexes were stable, and the systemic blood pressure was adequately maintained. Fig. 3 is a graph of the average values of the mean aortic blood pressure during the five experiments. The average amount of blood transfused was 1,450 ml., while the average hematocrit rose from a preoperative level of forty-two to a postoperative value of fifty-one. This hematocrit rise is similar to that encountered in the control series. The blood volume remained within 15 per cent of the preoperative level in two dogs tested. There was no change in the serum levels of sodium, potassium, carbon dioxide, and chloride or in the plasma proteins. Free plasma hemoglobin levels increased in all animals to the neighborhood of 250 mg. per cent, twice the level observed in the control series. Platelets decreased to 25 per cent of the preoperative level in one animal tested.

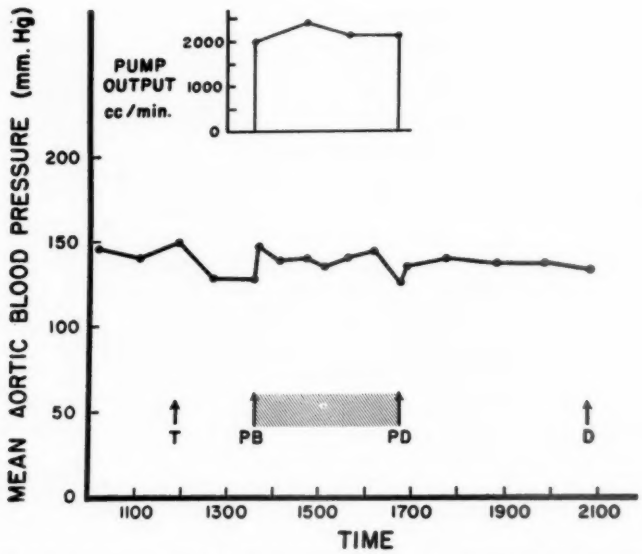

Fig. 3.—Graph of mean aortic blood pressures plotted from the average values observed in five consecutive nonpulsatile perfusion experiments. The cross-hatched area from PB to PD represents the three-hour period of nonpulsatile perfusion of the pulmonary circulation; T, the time of thoracectomy; and D, the time experiment discontinued. Note that arterial tension is adequately maintained throughout the procedure.

In four experiments gas analyses of arterial whole blood were performed on samples drawn at the time the animal was anesthetized and again after two and one-half hours of nonpulsatile perfusion of the pulmonary circulation. Arterial oxygen saturation remained above 95 per cent. The average drop in the carbon dioxide content (from 21.3 to 18.0 mM. per liter) was of the same magnitude as that seen in the control experiments where it was shown that the pH concomitantly fell to the neighborhood of 7.2. It is felt that the drop in carbon dioxide content and in pH are manifestations of a metabolic acidosis due to causes other than by-pass, since in control experiments we have observed the same lowered levels in carbon dioxide content *immediately preceding* the institution of cardiac by-pass; during by-pass there was no further lowering. Certainly it can be said that for a period of three hours a nonpulsatile flow

through the lungs is compatible with good oxygenation and good carbon dioxide elimination.

Electrocardiographic tracings were taken before, during, and after the perfusion in three experiments. The main change noted was transient inversion of T waves which is often precipitated by minor procedures in dogs.

Clinically, the lungs subjected to nonpulsatile perfusion showed no abnormalities. During the perfusion in all experiments the lungs remained easily inflatable with normal coloration and consistency. At no time in any experiment of the test and control series was there any evidence of pulmonary edema. The one long-term survival test animal was sacrificed four months after operation. At this time the lungs were grossly and microscopically normal.

DISCUSSION

Although the number of test experiments (five) described here is small, the results are consistent. It would appear that the lesser circulation can be artificially maintained in the dog using either pulsatile or nonpulsatile flows; that either type of flow is compatible with the normal respiratory function of the lung and leads to no permanent alteration of circulatory dynamics.

In contrast, preliminary data from three experiments suggest that a pulsatile flow is preferable for adequate perfusion of the greater circulation. Left heart by-pass with pulsatile perfusion of the systemic circuit for two hours allowed maintenance of normal arterial blood pressure with transfusion of blood not in excess of operative losses. However, when a nonpulsatile flow was used to perfuse the systemic circulation there rapidly occurred a persistent hypotension which did not respond to infusion of blood in amounts four times the operative losses. This hypotension was responsive to relatively small doses of Neo-Synephrine Hydrochloride. Before definite recommendations as to the type of pump outflow essential for adequate artificial maintenance of the systemic circulation can be made, further experimental data must be obtained.

SUMMARY

Techniques and apparatus for the nonpulsatile perfusion of an entire, intact circulation in dogs are described.

The experimental data obtained indicate that during right heart by-pass artificial maintenance of the intact pulmonary circulation is compatible with normal pulmonary function using either a pulsatile or nonpulsatile flow.

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ROENTGEN RAYS AND WOUND HEALING

An Experimental Study

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THE treatment of advanced cancer has become, in many instances, a combined irradiation-surgical problem. Certain neoplastic conditions merit preoperative therapy to increase chance for cure, even when surgery is the primary mode of therapy. In other instances tumors deemed inoperable because of extent of local growth may be converted to lesions that are technically resectable. In situations such as these, the effect of radiation therapy on the healing ability of a subsequent surgical wound is of great importance.

The success of surgery in achieving the specific aim for which it is intended demands, in most instances, relatively prompt and firm healing of the wounds produced. It has been frequently observed that irradiated tissues heal less kindly than comparable normal tissues. This is true both of wounds produced in tissues recently irradiated and wounds in tissues that were irradiated many years previously. The optimal time between preoperative radiation therapy and operation, in regard to wound healing, has not been established. Clinicians usually suggest a minimum delay period of six to twelve weeks. It is usually stated that surgery should be delayed at least until erythema of the skin has subsided.

There are, then, two unanswered questions of clinical importance: (1) How great is the effect of x-ray treatment in the therapeutic range on the rate of attainment of wound strength as compared to wounds in untreated tissue, and (2) within practical clinical boundaries, how long after irradiation of tissues is the deleterious effect on wound healing least marked?

Experimental work by Haberland as early as 1923 showed the retarding effect of x-ray treatment on wound healing.[1] Several workers felt that wound healing was stimulated by x-ray and radium treatment in a very low dosage range.[2-5] This is similar to findings with ultraviolet irradiation. It has been suggested that this is due to production or release of various intercellular enzymes (''proliferation promoting intercellular hormones''). Except for those very low dosage experiments, all other work demonstrates some delay in wound healing when irradiation is applied at the time of, shortly before, or within forty-eight hours of, wound production.[1, 5-9] The effect of irradiation on healing was studied in skin incisions or surface defects and usually did not involve deeper layers or coapted wound surfaces. The methods of

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study were, for the most part, gross inspection, measurement of surface epithelization, or histologic studies of the wounds. Tensile strength of the healing wound was measured by Dobbs,[5] using excised strips of abdominal wall.

All of these studies have been amply reviewed in detail by Arey[11] and by Pohle.[7, 8, 10] The previous data collected in this field do not fully answer our questions for the following reasons:

1. Observations on the epithelial growth of skin have no direct bearing on strength attained by a surgical wound.

2. Histologic interpretation of rate and degree of healing, although of definite value, is an unsatisfactory means of measuring wound strength.

3. The wounds in the healing studies referred to involved skin only and often were open wounds in which the margins were not coapted as in clinical surgical wounds.

4. The radiation used was either not translatable into present-day dosage factors or was much below the therapeutic range for neoplasma.

5. There were no studies in which irradiation preceded surgery by any more than three weeks. Thus there was no comparison with the usual clinical situation.

Therefore, a plan of study was formulated in which wounds comparable to clinical wounds were produced. These were made at varying times after irradiation was administered in a single exposure to the proposed wound site and at a dosage level comparable to those used in clinical therapy. Although it was recognized that a single high dosage exposure did not correspond to the usual clinical procedure, it was felt that it was best to begin these studies in this manner in order to provide a reproducible, definite, and serious level of damage to the tissue. The rate of healing in terms of wound strength was determined by means of measurements in millimeter mercury of the pressure required to reach the separation threshold of these wounds. Histologic studies were carried out in conjunction with these experiments.

PROCEDURE

Female white Wistar rats weighing 150 to 175 grams were used. Their diet, Purina laboratory chow, contained over 23 per cent protein by weight. Intraperitoneal Nembutal was used for anesthesia (approximately 6 mg. per 100 Gm.) during administration of irradiation and of wound production.

The standard irradiation field was a 3 by 2 cm. field centered over the midline of the abdomen with the xiphoid process marking the superior border of the field. The factors were: 100 k.v., 6 ma., 1 mm. aluminum filter, half value layer 18 mm. aluminum, 15 cm. target skin distance, 2,000 r. (measured in air). Since a series of measurements of abdominal wall thickness in this region all fell between 2 and 3 mm., depth dose calculations revealed that the peritoneum received a dose 96 per cent of the air dose, or 1,920 r.

The standard wounds were produced after careful skin preparation. All materials used were heat sterilized. The wounds were longitudinal and were placed 1 to 2 mm. inferior to the xiphoid process. The incision was carried

through the muscle layers just to the left of the linea alba and included the peritoneum. The wounds were 2.1 to 2.4 cm. in length. Closure was accomplished by three evenly spaced No. 34 stainless steel wire sutures placed through all layers and tied so as to achieve approximation without strangulation. The fresh wound was then covered with a protective layer of collodion.

The rats were divided into seven groups of thirty-two to forty animals each, one group serving as a control. Except for this control group all were given the standard irradiation described. The irradiated field was then outlined with marking material.

The standard surgical wounds were then produced. In one group the wounds were produced immediately. In the other groups they were produced one, three, five, eight, and twelve weeks following irradiation, respectively.

To test the tensile strength of the wounds produced, the animals in each of the larger groups were sacrificed (ether) in subgroups of four or five animals each at two, four, six, eight, ten, fifteen, twenty, and thirty days following surgery. The sutures were carefully removed at this time.

The method of Kobak and associates[12] was used to determine the tensile strength of the wounds. The intra-abdominal pressures at which the wounds separated were determined by increasing the pressure in a thin rubber balloon introduced on a catheter into the peritoneal cavity through a small incision in the lower abdomen. A heavy silk purse-string suture was placed in the abdominal wall at the site of exit of the catheter to preserve the integrity of the abdomen at this point. The modification and measurement of pressure were accomplished by means of a mercury manometer system similar to that used in clinical sphygmomanometers.

Tensile strength curves of the healing in each group were then made by using the average strength recorded in the subgroups at each time interval studied.

One rat from each subgroup was also sacrificed at the same time as the animals tested and was used for histologic studies. The sutures were removed, the entire wound was excised, and the specimen was placed in 10 per cent formalin. These were embedded, sectioned in a routine manner, and stained with hematoxylin and eosin.

The control group of forty rats received no irradiation but had the standard wound produced as described. The animals were sacrificed in groups of four at the same postoperative intervals as in the other groups with the exception that a three- and a five-day group were also added.

A separate group of eighteen animals was used for study of the effect of the level of irradiation used on plasma proteins and hematocrit. Initial blood samples of 1 c.c. were obtained by intracardiac puncture under Nembutal anesthesia. Coagulation of the sample was prevented with heparin. One-half of the animals were then given the standard dose of irradiation described. The animals were sacrificed in groups of four (two irradiated, two control) at weekly intervals following irradiation. Blood samples were obtained at time of sacrifice by intracardiac puncture. The plasma was separated by centrifug-

ing the samples in Wintrobe hematocrit tubes for 30 minutes at 1,500 r.p.m. Plasma protein levels were determined on the samples by the copper sulfate, specific gravity method.[13]

Animals of all groups were weighed at intervals to determine changes incident to irradiation and surgery. They were also weighed at time of sacrifice. The intraperitoneal organs were examined at this time, also, for gross radiation changes.

RESULTS

The general effects of anesthesia on nutrition were detectable as demonstrated by weight measurements of the control group and the nonirradiated animals in the blood study group. All of these animals maintained their weight and all weighed the same or more at time of sacrifice than before anesthesia.

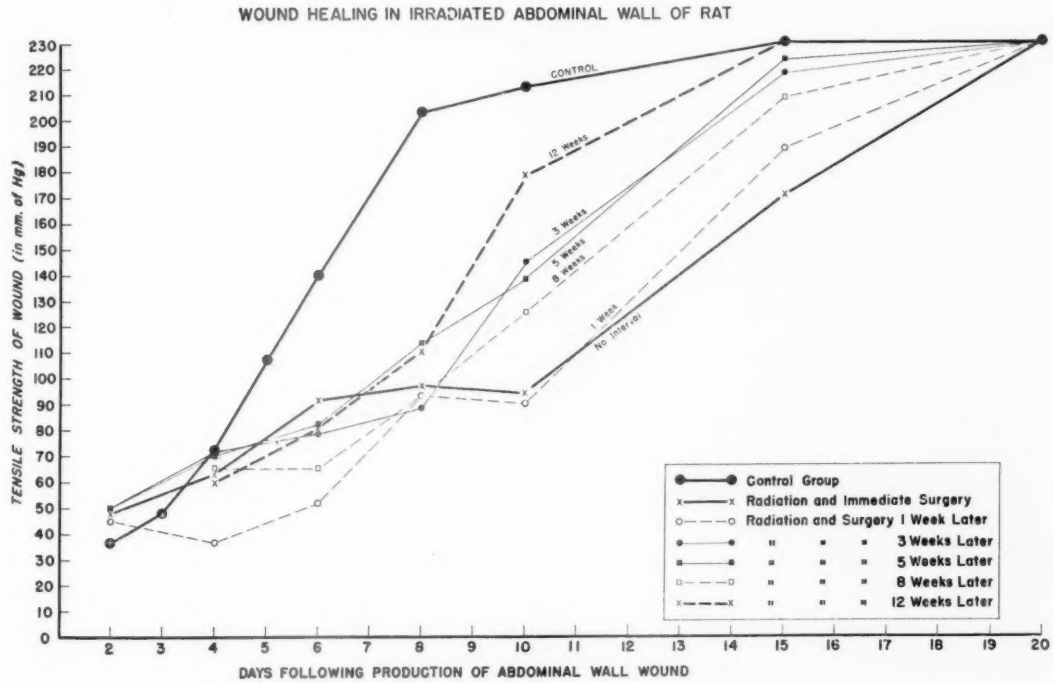

Fig. 1.

The weight measurements in the groups receiving irradiation were in contrast to this. Although there was some individual variation, most animals lost weight or maintained subnormal weight for the first two weeks following irradiation.

The animals in Group 1 (irradiation plus immediate surgery) experienced an average weight loss of 10 per cent of their original weight in the postoperative period. By three weeks following irradiation in the other groups the animals had in general regained their preirradiation weight and thereafter continued to gain at the normal rate. Except for Group 1 and Group 2 (irradi-

ation plus surgery in one week), all other animals maintained or gained weight in the postoperative period.

Blood studies revealed no significant changes in hematocrit following irradiation. The plasma proteins were maintained at a constant level in the nonirradiated control animals used in the special study. The irradiated animals had a drop in plasma proteins averaging 1 Gm. per cent for the first two weeks, but the proteins returned to preirradiation levels by three weeks and remained there at three and one-half, four, and five weeks after irradiation.

Wound infections were no problem. There was a collection of cloudy fluid in the abdominal wounds of three animals and these were discarded from the study. All three were in the two groups operated upon within one week of irradiation. There were several animals in each group that demonstrated slight superficial ulceration at the site of the wire sutures. The wound strength in each case was in the same range as the others in the same subgroup at that time. All other wounds healed well. There were no radiation changes discernible by gross examination in the stomach, bowel, or liver of the animals studied.

The measurement of tensile strength of the wounds was quite satisfactory, as the end point in the majority of cases was definite. The wounds separated quite suddenly in all instances except for some of the early wounds that separated at a pressure of less than 50 mm. Hg. It was impossible to determine the tensile strength of wounds able to withstand over 220 to 230 mm. Hg pressure. At this level other portions of the abdominal wall were unable to withstand further increase in pressure and separated or herniated. All values between 50 and 220 mm. Hg were quite satisfactory. It was believed that these limitations at the extreme limits of the curves were not detrimental to graphing the entire phase of healing and attainment of tensile strength.

The average values for tensile strength of wounds in terms of time following production are shown in Table I for both control and irradiated groups. The control group showed a rapid rise in wound strength from day four through day eight postoperatively. The changes prior to day four (which is usually considered the lag period in normal wound healing) were not standard due to the inaccuracy of this method at pressures of less than 50 mm. Hg. From the eighth to fifteenth day following surgery the wounds showed a slight further increase in strength as shown by Table I. It is seen that the major portion of the tensile strength was attained, however, by the eighth day.

The values and curves produced for Groups 1 and 2 (immediate surgery and surgery following irradiation by one week) were practically identical. Instead of a rapid rise in strength, as occurred in the control group, there was a slow, progressive increase in tensile strength that reached its maximum at twenty days. The level attained at eight days in the control group was not attained in these groups until somewhere between fifteen and twenty days. It should be recalled, however, that these two groups were operated upon in the short time interval shown to be associated with some weight loss and hypoproteinemia following irradiation.

TABLE I. AVERAGE VALUES FOR TENSILE STRENGTH (MM. HG) OF EACH SUBGROUP

DAYS POSTOPERATIVE	CONTROL GROUP	GROUP 1 (IRRADIATION AND IMMEDIATE SURGERY)	GROUP 2 (SURGERY 1 WEEK POSTIRRADIATION)	GROUP 3 (SURGERY 3 WEEKS POSTIRRADIATION)	GROUP 5 (SURGERY 5 WEEKS POSTIRRADIATION)	GROUP 8 (SURGERY 8 WEEKS POSTIRRADIATION)	GROUP 12 (SURGERY 12 WEEKS POSTIRRADIATION)
2	37 ± 3	48 ± 20	45 ± 10	50 ± 5	50 ± 20	—	—
3	48 ± 10						
4	72 ± 12	63 ± 20	37 ± 5	71 ± 15	70 ± 10	65 ± 10	60
5	107 ± 10						
6	140 ± 15	91 ± 13	52 ± 15	78 ± 7	82 ± 3	65	80 ± 20
8	203 ± 15	97 ± 15	93 ± 15	88 ± 15	113 ± 12	95 ± 20	110 ± 10
10	213 ± 7	94 ± 5	90 ± 15	145 ± 20	138 ± 15	125 ± 17	178 ± 10
15	230 +	170 ± 10	188 ± 12	218 ± 15	223 ± 10	208 ± 10	230 +
20	230 +	230 +	230 +	230 +	230 +	230 +	230 +

The groups in which wounds were produced three, five, and eight weeks after irradiation had almost identical curves of tensile strength in terms of time following surgery. Instead of a rapid healing phase as in the controls, these wounds increased in tensile strength gradually, reaching the maximum range in fifteen days. It is of interest that these three curves were so similar in spite of the fact that one of these groups was operated upon at the time of the height of skin reaction from the irradiation.

The group operated upon twelve weeks following irradiation had a healing curve which demonstrated a more rapid increase in tensile strength than in the other irradiated groups. This difference, although definite, was not great when compared with the control curve (see Table I).

Histologic studies of the control wounds showed the usual early appearance of wandering cells and fibrin at the wound site. The surface epithelium covered the coapted skin defect within three days. By this time fibroblasts appeared in the wound area. Five days after wound production these cells were more numerous and some collagen fibers were present, in addition to a network of fibrin. The fibroblasts and collagen increased in quantity and maturity during the five- to ten-day period. From this time until twenty days following surgery, the collagen network gradually increased in density. The major histologic changes occurred in the period in which major changes in tensile strength occurred.

Histologic studies of the wounds in previously irradiated tissue demonstrated epithelization in most instances just as quickly as in the control wounds. The early infiltration of cells and fibrin was decreased quantitatively in the most recently irradiated tissues. The appearance of fibroblasts and collagen fibers did not occur in any quantity until the eighth day in the two groups with no interval and a one-week interval between irradiation and surgery. In these same two groups the wounds appeared at twenty days to be very similar to the control wounds at ten days in regard to quantity and quality of collagen and fibroblasts. The major advances in wound healing, histologically, were between the eighth and the twentieth day, which corresponds well with the tensile strength curves for these two groups.

The histologic changes in groups operated upon three, five, and twelve weeks following irradiation showed little or no suppression of cellular response

as compared with the control group, and the wounds of these three groups matured at a similar rate. The sections showed most of the fibroblastic and collagen activity to be from the eighth to the fifteenth day. The sections were quite similar to those of the control group at earlier intervals and, in general, concurred with the tensile strength healing curves. These wounds often appeared to be slightly more vascular than the comparable control wounds. All these histologic observations fit roughly into the pattern demonstrated by the healing curves in terms of tensile strength. None of the wounds was followed to the eventual complete maturation of the scar, but they were followed into the maximum strength range.

DISCUSSION

The basic situation produced in these experiments was analogous to our clinical problems in wound healing after irradiation. The wounds were composite in that all the tissue layers of the abdominal wall were incised. The irradiation administered in one treatment may be considered to be comparable to much higher dosages given in a fractioned manner over several weeks' time. They were definitely in the clinical dosage range.

The method used for determining the tensile strength of these wounds is similar to wound stresses that occur clinically. There are certain disadvantages to the method, however. The inaccuracies of the determinations when the pressure disruption was less than 50 mm. Hg prevented any analysis of wound strength changes in the first four days after operation. This encompasses the so-called lag-period in wound healing. The upper limitations of this method in regard to tensile strength measurements were based on the fact that the wound reached a strength equal to other portions of the abdominal cavity before complete healing occurred. In the normal wounds this level was reached on the fifteenth day, at which time, it is stated by other workers,[14] the wound has reached maximal strength. This control curve compares favorably with healing studies by other methods.

The irradiated animals all showed delay in wound healing under conditions of the experiment, but all groups demonstrated a final wound strength comparable to nonirradiated controls. The data show greater speed in attaining strength if operation is delayed until three weeks after irradiation, instead of being performed immediately or one week following irradiation. Under the conditions of this experiment this difference may not be a direct local effect of the radiation, as the animals in the early period after irradiation were in suboptimal nutritional state as measured by weight changes and plasma protein levels. The deleterious effect of hypoproteinemia alone on wound healing has been well demonstrated by Kobak and associates.[12] Vitamin C is another nutritional factor of great importance in wound healing, but this was ignored in this study as the rat normally is able to synthesize its own supply of this vitamin.

There seemed to be little difference in rate of wound healing in the group in which operation was delayed eight weeks after irradiation in comparison to

the groups in which the delay was only three weeks or five weeks. This is of some interest as skin reaction after x-ray treatment was at a peak in the three-week group. This suggests quite strongly that the erythema stage in the post-irradiation period is not significant in wound healing in the rat. The nutritional state of these groups was satisfactory as shown by the weight and plasma protein studies.

In the group in which there was a twelve-week delay before surgery, the wounds healed more quickly, as measured by tensile strength, than any of the other irradiated groups. The difference from the other irradiated groups when compared to the controls, however, was not great. These data suggest that there is little to gain from the healing standpoint by waiting more than three weeks after irradiation to carry out surgical procedures. It must be remembered that these data were obtained from study of wounds in the rat and the irradiation was given in one dose. We plan to repeat a portion of this work using a standard fractionated course of irradiation.

SUMMARY AND CONCLUSIONS

Young rats were subjected to standard abdominal incisions at times after irradiation of the wound areas varying from no interval to three months later. The irradiation administered in the preoperative period was in the clinical therapeutic dosage range and the wounds were comparable to clinical laparotomy incisions. Studies of the rate of healing of these wounds in terms of tensile strength were carried out and showed that all wounds reached the maximal strength range, although there was some delay in the rate of attainment of this strength by the irradiated wounds. Delay in healing was most marked in the wounds receiving irradiation immediately or one week before surgery. The difference in the healing curves between tissues irradiated three weeks, five weeks, eight weeks, and twelve weeks prior to surgery was not great. Nutritional and histologic studies were carried out and these confirmed data obtained in the measurement of tensile strength of the healing wounds.

These data suggest that healing of surgical wounds in recently irradiated tissue is impaired, in a practical sense, only in terms of rate of healing and not in terms of final wound strength. The data also seem to demonstrate little or no practical advantage in delaying surgery more than three weeks after irradiation. The presence or absence of irradiation-induced skin erythema, per se, seems to have little effect on the rate of wound healing in the rat.

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METASTATIC TUMORS IN THE BREAST

With a Report of Ten Cases

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TUMORS in the breast are universally accepted to be primary in origin. The possibility of a metastatic tumor in the breast is very seldom entertained in a differential diagnosis. This dates back to the time of Virchow, who believed that most organs which show a strong tendency to develop primary malignant tumors are seldom the site of secondary tumors.[1] The subject of metastatic tumors in the breast is not mentioned at all in modern textbooks of pathology or surgery. Dawson[2] in 1936 found only ten histologically proved cases in the literature and added one of his own. In 1942 two cases were reported from the Brooklyn Cancer Institute.[3] In 1947 De Alvarez[4] added another case, and in 1948 Speert and Greeley[5] reported one case, making a total of fifteen cases reported in the literature up to the present writing. To these we wish to add ten additional cases studied at the Brooklyn Cancer Institute since 1942.

Table I. Summary of Ten Cases of Metastatic Tumors in the Breast*

Case	Sex, Race, and Age	Primary Site	Histology	Breast	Axilla	Other Secondary Growths
1.	F, W, 28	Left shoulder	Malignant melanoma	Bilateral	Bilateral	Abdominal wall, peritoneum, both ovaries, liver, lungs†
2.	M, W, 60	Anterior chest wall	Malignant melanoma	Right	Right	Lungs
3.	M, W, 55	Left shoulder	Malignant melanoma	Left	Left	Scalp, lungs, pericardium, liver, spleen, pancreas, mesentery, left testis†
4.	F, N. 46	Ovary	Papillary adenocarcinoma	Right		Uterine cervix
5.	F, W, 45	Ovary	Adenocarcinoma	Left		Generalized abdominal metastasis, ribs
6.	F, W, 48	Right kidney	Clear cell carcinoma	Left		Lungs, left thigh, right buttock
7.	M, W, 67	Left kidney	Adenocarcinoma	Right		Lungs, left subclavicular region, fifth rib
8.	F, W, 43	Thyroid	Anaplastic carcinoma	Bilateral		Lungs, subcutaneous nodules of chest and abdomen
9.	M, W, 43	Prostate	Carcinoma	Right		Inguinal, mesenteric, and retroperitoneal glands, capsule of liver and spleen, serosa and muscularis of intestines, perivascular lymphatic spaces of lungs†
10.	F, W, 42	Fundus of uterus	Carcinoma	Right	Left	Left supraclavicular and bilateral inguinal glands, vaginal wall

*Metastatic tumors from the opposite breast were excluded.
†Autopsy obtained.

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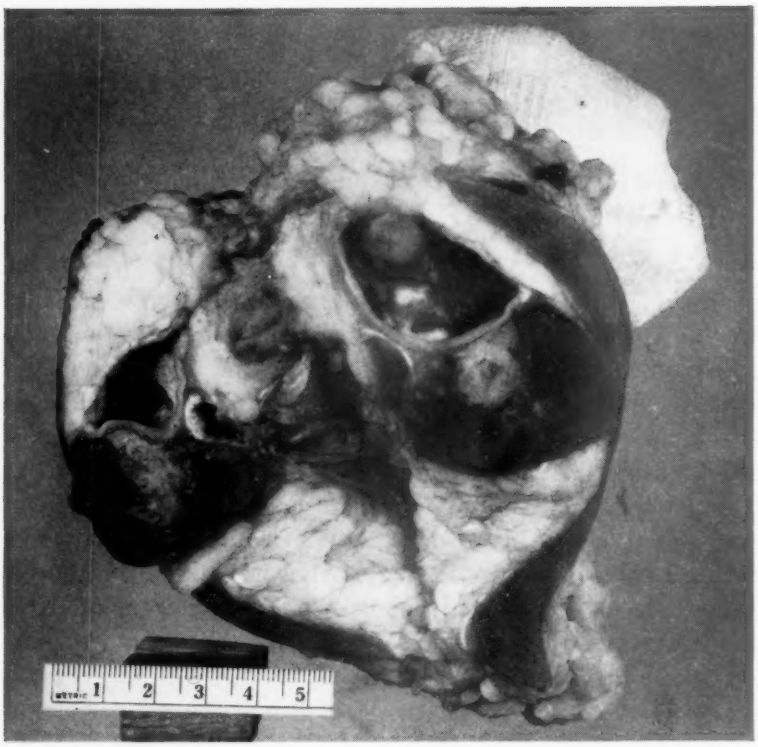

Fig. 1 (Case 4).—Gross specimen of metastatic papillary adenocarcinoma of the breast of ovarian origin.

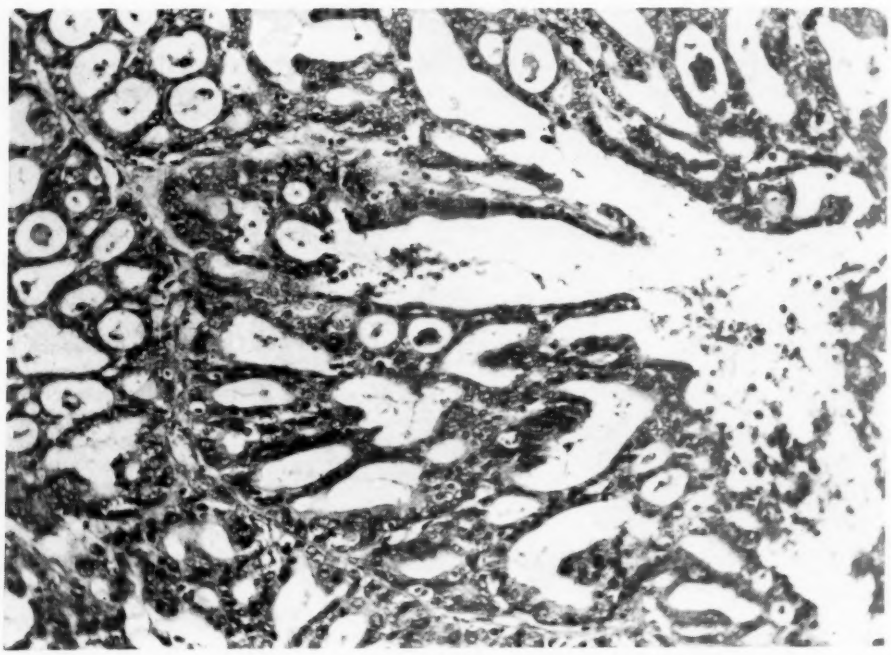

Fig. 2 (Case 4).—Photomicrograph showing metastatic papillary adenocarcinoma of the breast of ovarian origin (×220).

Analyzing the fifteen cases reported in the literature and the ten new cases reported here, we find that of twenty-four patients about whom information is available, eighteen were women (75 per cent) and six were men (25 per cent). The oldest patient was 67 years, the youngest 16 years, and the average age was 44 years. All of our twelve patients were white except one, who was a Negress. In eight cases both breasts were involved. Nine involved the right breast and seven the left. The axilla was involved eight times. Of the twenty-five cases, seventeen were carcinoma (68 per cent), four malignant melanoma, one myxosarcoma, one fibrosarcoma, two lymphosarcoma. The primary lesions in the twenty-five cases of metastatic tumors in the breast were as follows: stomach five, liver one, kidneys three, prostate one, ovaries four, uterine cervix two, fundus of uterus one, thyroid one, mediastinum one, os pubis one, opposite breast one, skin four (melanoma of left shoulder two, chest wall one, left arm one).

Fig. 3 (Case 8).—Cut section of gross specimen of metastatic carcinoma of the breast of thyroid origin.

Diagnosis of a metastatic tumor in the breast is not always possible. In the absence of symptoms a small primary lesion may be overlooked on routine physical examination. Even when an extramammary lesion is found, a double primary or a metastatic growth has to be considered. Histologically it is not always possible to diagnose a metastatic lesion in the breast when the tumor is highly anaplastic. Even when it is diagnosed, the primary site is not always determined from the histologic study.

Fig. 4.

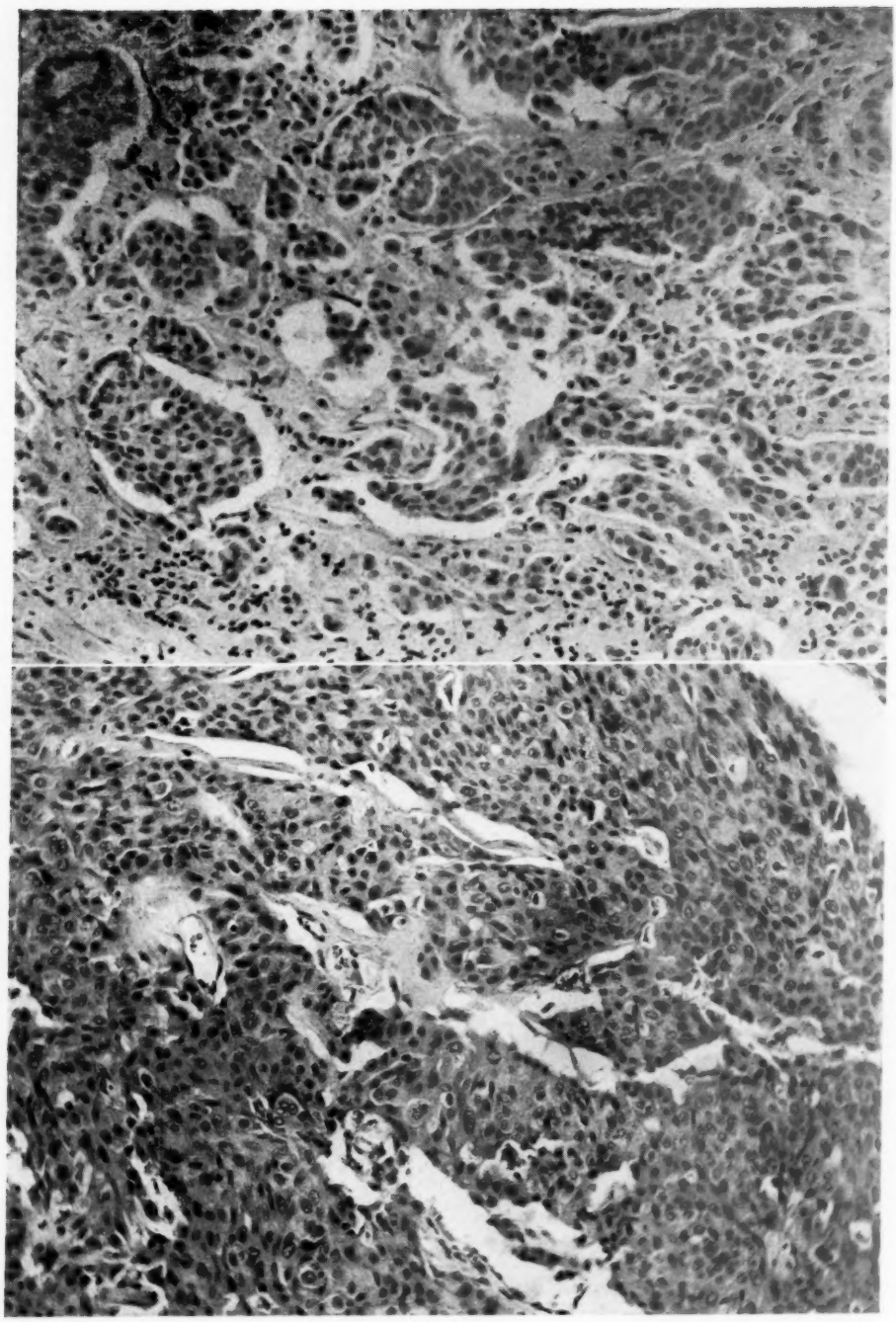

Fig. 5.

Fig. 4 (Case 8).—Photomicrograph showing metastatic carcinoma of the breast of thyroid origin (×200).

Fig. 5 (Case 8).—Photomicrograph showing primary anaplastic carcinoma of the thyroid (×100).

Fig. 6.

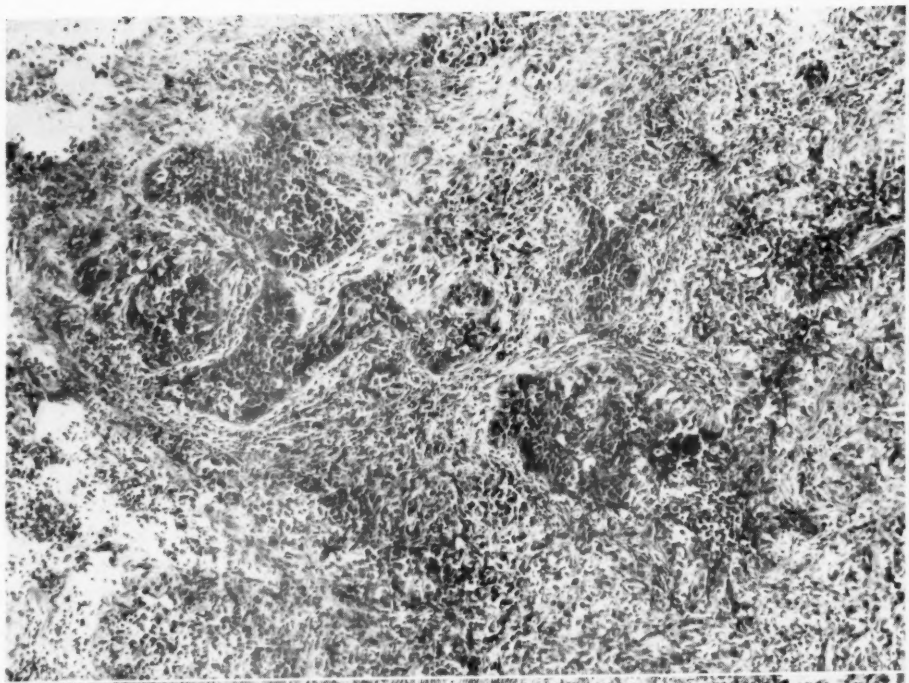

Fig. 7.

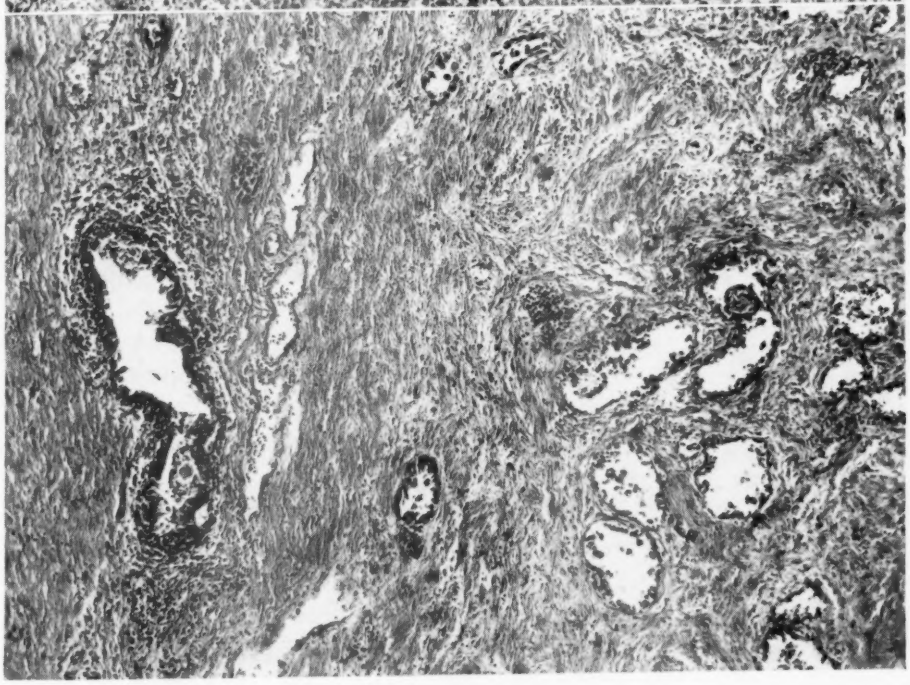

Fig. 6 (Case 9).—Photomicrograph showing metastatic carcinoma in the breast of prostatic origin (×110).

Fig. 7 (Case 9).—Photomicrograph showing primary carcinoma of the prostate (×110).

Case 9 in our series was that of a patient who had a metastatic tumor of the breast of unknown origin with no other subjective or objective clinical findings to suggest its origin. In spite of an exhaustive laboratory work-up and numerous consultations, the diagnosis was not established until an autopsy revealed a primary tumor of the prostate. Case 4 was that of a patient admitted for a tumor in the breast. The patient was in excellent condition. There were no other clinical findings on examination. However, the record and slides from another hospital revealed that she had been operated on four years previously for a papillary carcinoma of the ovaries and had received radium treatment for a metastatic carcinoma of the cervix of ovarian origin. On admission the patient was free from any recurrence of the cervical carcinoma. The abdomen was soft with no palpable tumefaction and no ascites. The pathologic report of the breast tumor was papillary adenocarcinoma of ovarian origin.

From our own observation (twelve cases) we found that metastatic tumors in the breast are less fixed to the surrounding tissue than primary tumors, or are freely movable. However, the consistency is that of a primary malignant tumor. The overlying skin is of normal texture, not dimpled, and not adherent to the tumor. Pain in the breast was absent in all our cases. The size of the tumor varied from 1 to 4 cm.

The treatment of choice is the removal of the primary lesion if possible, the excision of the metastatic growth or a simple mastectomy, followed by radiation therapy.

The prognosis in metastatic tumors in the breast is very grave. Most of our cases were terminal and the patients died within six months. The patient in Case 4 in our series is the only one who is living and well four years after the removal of a primary carcinoma of the ovaries and one year after a simple mastectomy for a metastatic growth, followed by radiation therapy. She is doing her own housework and is attending our breast clinic.

It is realized that no conclusion can be drawn from such a small series of cases of metastatic tumors in the breast. However, it may serve as a nucleus to stimulate further reports on this subject.

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SIMULTANEOUS RUPTURED ECTOPIC AND INTRAUTERINE PREGNANCY

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SIMULTANEOUS ectopic and intrauterine pregnancies occur about once in every 30,000 pregnancies.[1] This report covers a ruptured ectopic pregnancy with survival of the intrauterine fetus and subsequent normal delivery. The coexisting uterine and extrauterine pregnancy is not extremely rare, although uncommon in the experience of any one man. According to H. P. Miller[2] the total number of reported cases was 395 in 1948. The condition was recognized as far back as 1722.

The diagnosis of tubal pregnancy in the presence of an intrauterine one is understandably difficult. Vaginal bleeding is likely to lead to the suspicion of a threatened abortion, while cases like ours, which show no spotting, are even more confusing.

Studdiford and Speck[3] note "a review of the literature shows that the most favorable outcome results when the ectopic pregnancy undergoes rupture without disturbing the uterine gestation. In such cases, the ectopic pregnancy manifests itself first, is recognized, and is promptly brought to surgery."

It appears that the group of cases which has yielded the greatest mortality is marked by a preliminary abortion, delivery, or discovery of the uterine pregnancy followed by the rupture of the ectopic pregnancy. The mortality following this sequence of events has been high and in the neighborhood of 20 per cent, according to Henry H. Faxon.[4]

Most often, the ectopic pregnancy ruptures first, followed by a spontaneous abortion or miscarriage.[5] However, as in our case, after the ectopic pregnancy is operated, the intrauterine one may go to term.[6-9]

Our patient was A. Y., aged 24 years, para iii, who had a normal delivery in 1946 and again in 1947. Her last period was on Aug. 12, 1951. She was admitted to the surgical service of the Monmouth Memorial Hospital, Long Branch, N. J., on Nov. 14, 1951, with abdominal pain and in shock. Five days previously she suffered a sudden abdominal pain, referred to both shoulders, which was so severe that she fainted. However, she recovered from this attack and, except for persistent nausea and occasional vomiting, seemed better and was ambulatory until about one hour before admission, when she fainted again and the abdominal pain returned.

Examination on admission revealed a pale, dyspneic, 24-year-old white woman in acute distress and restless, with a temperature of 100° F., pulse 120, and blood pressure 100/60. Her abdomen was distended and doughy, with a vague mass above the pubis extending into the right lower quadrant. Pressure over this mass produced pain in both shoulders and the patient complained that

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it made her feel as if her "breath was cut off." Vaginal examination showed a soft bluish cervix which was not dilated, but seeped clear fluid which was considered to be probably amniotic fluid. Lateral motion of the cervix caused pain and there was a soft fullness anterior and to the right of the lower uterine segment, which was thought to be blood. The fundus could not be mapped out. The right lower quadrant mass was taken to be a ruptured ectopic pregnancy and, while the probability of an intrauterine pregnancy was considered, it was decided to do a laparotomy because of obvious intra-abdominal bleeding.

The blood count showed 35 per cent hemoglobin, R.B.C. 2,000,000, W.B.C. 9,000, polys 81 per cent, lymphocytes 19 per cent. Two thousand cubic centimeters of blood was given before, during, and just after the operation, which was performed within an hour of admission and disclosed the peritoneal cavity filled with free blood and clots. The uterine fundus was soft, symmetrical, and enlarged to the size of a three months' pregnancy. The left tube was buried in the posterior surface of the broad ligament so that the fimbriated end was not visible. The ovary was small and buried in the same mass of inflammatory tissue. The right ovary contained a corpus luteum and the right tube contained a placental mass and showed a rupture in its distal one-third. A fetus, the size of a ten-week pregnancy, was attached to this mass by an umbilical cord, but floated free in the surrounding blood. The right tube and contents were removed and the abdomen closed. The patient did well, was out of bed thirty-six hours after surgery, and was discharged on the eighth day with a wound healing by primary intention and a blood count of 84 per cent hemoglobin, R.B.C. 4,500,000, W.B.C. 7,600, polys 71 per cent.

Samuel J. King[8] writes:

> The combination of intrauterine and extrauterine pregnancy is probably identical with a multiple pregnancy except that, instead of the implantations occurring normally within the uterine cavity, one or more of the fertilized ova reach the intrauterine spaces where they commence normal development, whereas the remaining one or more become simultaneously implanted outside the uterus—that is, in the fallopian tube or in the ovary or at some site within the abdominal cavity. The expression "one or more" is used because a limited number of cases have been reported where coexisting intrauterine and extrauterine pregnancies have occurred in which more than one fertilized ovum has become implanted either within or without the uterine cavity. The extrauterine pregnancy may produce the typical symptoms or signs of early ectopic pregnancy at four to twelve weeks, usually at about eight weeks, when internal hemorrhage or tubal rupture occurs, suggesting the necessity of prompt surgical relief; or the extrauterine pregnancy may fail to cause the classical syndrome of the early weeks and proceed to develop to term, or near term, and even be productive of a viable, although not necessarily normal, fetus. The intrauterine pregnancy of this combination, for the most part, is no different from any other such gestation, it may abort or miscarry, with or without apparent cause, or it may proceed to term with delivery of a normal living infant.

COMMENT

Neither the extrauterine nor the intrauterine pregnancy of our case was remarkable, if considered separately. The interesting aspect is their simultaneous occurrence and the fact that the intrauterine pregnancy continued to term, a normal female infant being delivered spontaneously on May 2, 1952.

SUMMARY

1. A case of simultaneous ruptured ectopic and normal intrauterine pregnancy is reported.

2. The ectopic pregnancy ruptured at ten weeks and was successfully operated.

3. The intrauterine pregnancy went to full term and resulted in a normal child.

4. This not too infrequent condition is discussed in its several aspects.

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THE PYLORODUODENUM AND GASTRIC RESECTION

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(From The St. Catharines Clinic)

STATISTICS indicate that 70 to 90 per cent of those patients who have a poor result immediately following gastric resection for pyloroduodenal ulcer have a leak from the turned-in duodenum, and/or trauma to the pancreas, as the primary fault. This is always associated with a hard-to-handle ulcer. Therefore, if this ulcer-pancreas pathology could be disturbed as little as possible—and yet adequately treated—and if the duodenal closure could be made in anatomically normal and physiologically healthy tissue, the incidence of these two complications should be much reduced. And so, when the pyloro-duodeno-pancreatic area has been dangerously difficult to manipulate, separate, and suture, and when disease has been such that trauma to the pancreas appeared probable, I have solved the problem very satisfactorily, in three instances, by the following method (Fig. 1). (However, it is not commonly needed, but like many other procedures, it is most useful when most needed.)

After the position of the ampulla has been definitely determined (by either a tube, a probe, or a ureteral catheter in the common duct, or careful dissection with the index finger in the foramen of Winslow),* the intact duodenum just proximal to the ampulla is freed from the pancreas throughout its circumference, for a distance of 10 to 15 mm. It is then transected with or without clamps, and a clean, safe, and secure closure of the distal segment is made in healthy tissue. The cutting of the duodenum on the bias with the longer edge on the outer side, farthest from the pancreas, may give more duodenal tissue for closure when this is necessary. It may also produce a wall that necrotizes easily. The accessory pancreatic duct of Santorini is carefully looked for. The closure of the duodenum thus becomes the first procedure—and a planned and definitive one—which makes sure of the use of normal tissues early in the operation, rather than the forced using of the best tissues available after the duodenal pathology has been removed or otherwise dealt with—for example, after the Bancroft procedure (which really was first described by Finsterer) or that of Nissen, or Wilmanns, or Graham, or Wangensteen, or the catheter intubation as described originally by Welch and later by Priestley. In some patients the two-stage operation advocated by McKittrick is easier and safer.† The first stage thus becomes the radical, but necessary, part—but only a part—of the real over-all physiologic treatment which is medical and surgical combined, each of which augments the other.

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*Another way to determine the location of the ampulla is as follows: After the duodenum has been opened on the convex side at about the area of transaction, methylene blue is injected into the common bile duct through a hypodermic needle, inserted at a very definite angle to reduce the leakage, and then the duct is massaged. The appearance of the dye will show the location of the ampulla of Vater. In this way the common bile duct has not been opened or otherwise traumatized.

†I prefer to perform the second stage in eight to twelve weeks, rather than the six weeks advocated by him, during which time the patient is receiving good medical treatment for an active duodenal ulcer—because the patient still has an active duodenal ulcer and also still has an actively secreting pyloric mucous membrane. In this way a jejunal ulcer will not grow, and probably will not even start.

After the pylorus has been transected, the remaining and distal section of the pylorus and the remaining and proximal part of the duodenum are then incised longitudinally along the line of the antimesenteric border, and the lumen is laid open. This produces an oblong or square of gut wall covered with pyloric and duodenal mucous membrane, on which is clearly seen the ulcer (Fig. 2). This piece of tissue can then be carefully dissected and removed as desired, and not as dictated by necessity, as is the case if dissection is started in the proximal pyloric area, when it must be continued until usable duodenum is available for secure closure. If the posterior duodenal wall is too densely adherent, either by inflammatory or scar tissue reaction, or if the ulcer is too penetrating, dissection and trauma can be stopped at once without being influenced by having to yet close the duodenum—because it is already closed—and a section of the posterior duodenal wall, of varying size, including the ulcer but minus its secreting mucous membrane, can easily be left in situ on the pancreas (Fig. 3). Thus, trauma to the dangerous pyloro-duodeno-pancreatic area is minimum, if not completely absent. This piece of unremoved tissue can be removed from the peritoneal cavity, if so desired, by covering it with omentum. However, this is not necessary.

Fig. 1.—A lateral-oblique picture showing extensive scarring of the pyloroduodenal area. An acute exacerbation of pyloric obstruction occurring in a thirty-year ulcer history. Distal to this area on the lesser curvature of the duodenum is clearly seen the ampulla of Vater. The picture shows how anatomically normal and physiologically healthy tissue is available for closure of the duodenum distal to the ulcer area and proximal to the ampulla. However, there is not always as much available duodenum as is shown above, especially if active inflammation is present.

It is true that in some instances, without this procedure, the operator may be forced to progress as far distally on the duodenal curve for the closure as is here advised, but such a closure is not by design and may not be satisfactory. It is rather because he cannot stop with safety before this point has been

reached. However, if, by design, an attempt is made to start the dissection at the distal point in normal tissue (Figs. 1 and 2) and to progress in a retrograde manner toward the ulcer, it will often be found that manipulation and dissection will be easier and more definitive, because the anatomy is normal and inflammation is minimal. Trauma to the pancreas will also be minimal because the posterior pyloroduodenal wall can be left undisturbed.

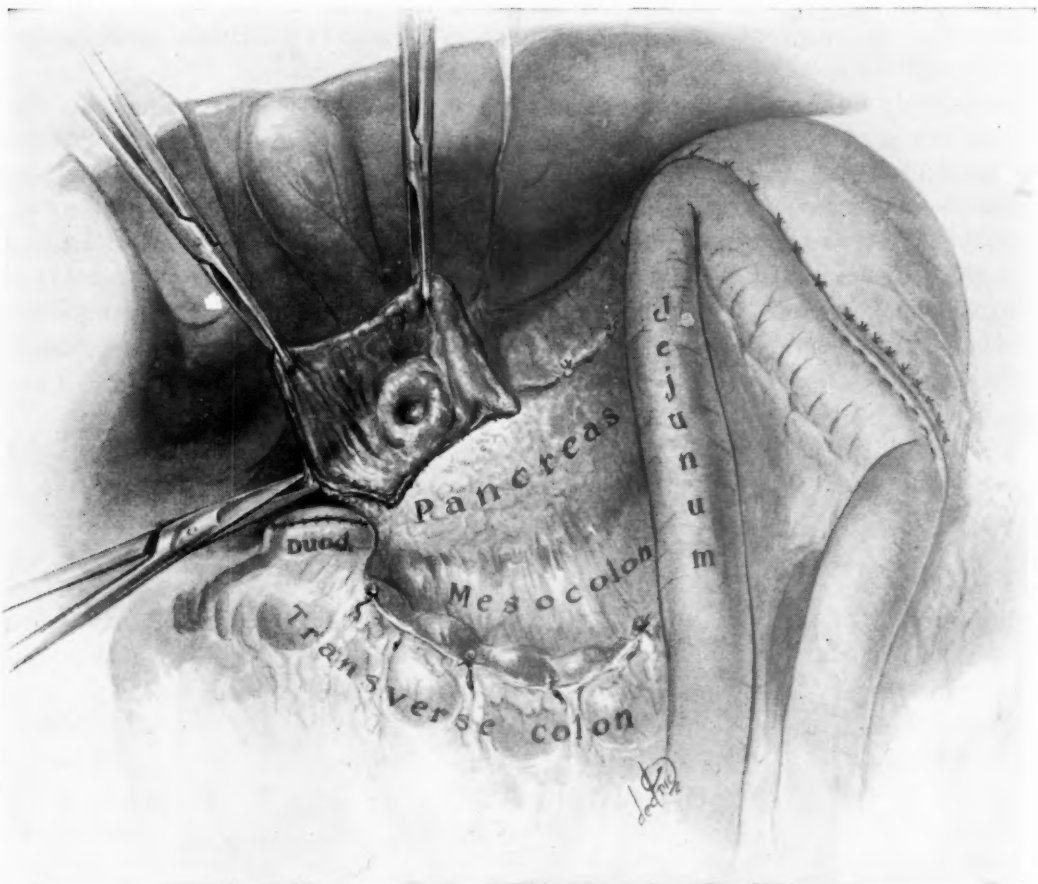

Fig. 2.—Illustration of the large pyloroduodenal square of gut being safely dissected away from the underlying pancreas. It shows clearly how dissection and trauma can be stopped immediately potential danger is seen, *without being influenced by having to yet close the duodenum*—which influence is always active when the duodenum is not closed. The gastrojejunal anastomosis is shown as completed. It is often beneficial to finish this proximal section of the operation before the distal section is started.

In certain cases it is thought by some that it is wiser to leave the ulcer in situ in the turned-in duodenum. This has often been associated with an unsatisfactory result even though an otherwise wide resection has been made, particularly if resection has been performed for an actively bleeding ulcer. If the ulcer is so left, it is physiologically quite different from leaving the ulcer area in, as herein described, because in the former instance the secreting surfaces of both the ulcer and the duodenum are left intact and a functioning surface remains. Thus an ulcer *may* reactivate and/or bleed again. However, in this procedure, neither the ulcer nor the duodenum has a secreting surface; it is merely a piece of nonfunctioning tissue quite separated from the duodenal

surface. The ulcer is really scar tissue replacement of serosa and muscle layer, without any mucosa. It is inert and dead tissue which can be removed from the peritoneal cavity, if so desired, by covering it with omentum. Thus the leaving of this orphan ulcer and adherent duodenal wall in place is not the same as leaving a potentially active ulcer in a functioning duodenal stump, and appears to be much safer.

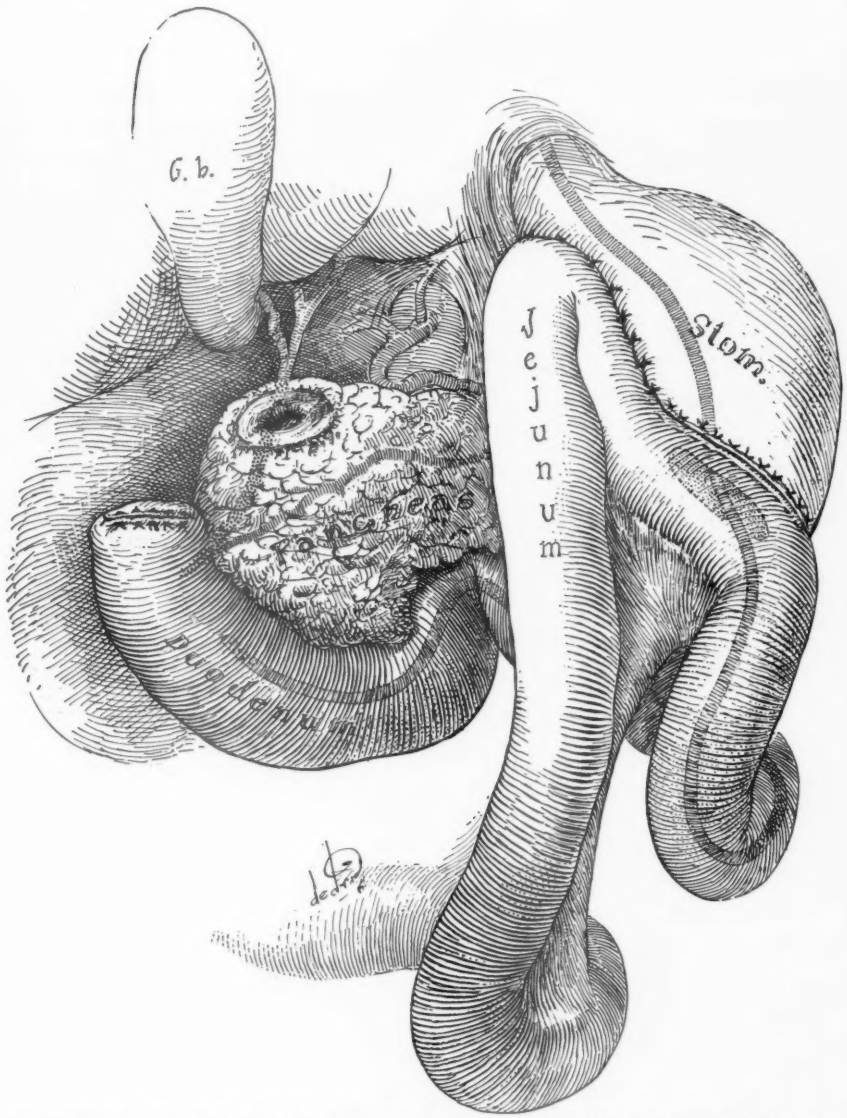

Fig. 3.—Illustration of the finished operation and the position which the nasal tube may assume in cases of a doubtful duodenal closure. The remaining ulcer and duodenal wall is here illustrated as a round area. This may be almost any shape because more wall than is here shown is almost always left. It is better to leave too much posterior wall than to take off too much. Note that the gastric contents enter the proximal duodenal-jejuno segment. Thus the preoperation physiology is more closely reproduced than it would be if the gastric contents entered the jejunum farther away and were immediately carried distally.

Although I have not yet had occasion to use this method of closing the duodenal stump in any case of resection for bleeding ulcer, it does present a method by which the bleeding duodenal ulcer might be clearly seen and better handled.

There would be several ways of closing the square of gut (Fig. 2), one of which would be to reduce the large quadrangle of tissue to a size which would allow the edges to be safely approximated with sutures, either with or without a dead space in the center, but preferably without. If a dead space or even a small potential space between the layers was left, and maybe filled with a hemostatic sponge material, and the mucous membranes were scarred and the suturing was made secure, the tamponade thus formed should successfully stop the bleeding.

SUMMARY

A beneficial method of closing the duodenal stump, and of satisfactorily handling the pyloro-duodeno-pancreatic pathology, in certain cases of gastric resection for pyloroduodenal ulcer, is presented for consideration. By it the closure of the duodenum is made in the anatomically normal and physiologically healthy tissue of the descending loop, just above the ampulla of Vater. It is thought wiser to sometimes do this as a planned and definitive procedure in healthy tissue, which is performed early in the operation before the ulcer is attacked, rather than to perform a makeshift closure, using the best available tissue, after the pathology has been removed. The potentially dangerous pyloro-duodeno-pancreatic pathology is thus minimally traumatized, but satisfactorily treated, by leaving a large section of posterior duodenal wall in situ at this area, minus its mucous membrane.

Although such a closure is dependent upon the anatomic variations of the duodenal curve, it is quite possible in the two most common types as described by Anson and associates. It is, of course, not applicable to every case, but it does seem to offer an additional, and a practical, and a satisfactory way of handling some cases of the difficult-to-close duodenal stump, associated with extensive periduodenal involvement. It has been of much value in three personal cases.

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THE EFFECT OF CORTISONE ON THE HEALING OF WOUNDS IN THE CARDIOVASCULAR SYSTEM

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THE administration of cortisone and ACTH has been noted to result in definite alterations in wound healing. Most previous studies have been made on wounds of the skin and subcutaneous tissue. Since patients upon whom operations are to be performed for cardiovascular deformities might be receiving these drugs, it seemed that a study of their effect on the healing of wounds of the cardiovascular system in animals might be of value. The purpose of this communication is to present an experimental study of the effect of cortisone on the healing of wounds of the aorta and myocardium.

In studies reported previously by various authors, the major change noted was a delayed appearance of fibroblasts, capillaries, and granulation tissue as a result of which the rate of gain of tensile strength in the wound was decreased 50 to 60 per cent as compared to the rate of gain in a normal wound. Ragan[1] and Howes[2] and their associates have reported a series of experiments in which rabbits were given cortisone in various doses for periods up to eleven days. The rate of healing of open skin wounds was studied, and a marked delay in the appearance of granulation tissue as compared to that in the control animals was noted. Blunt and associates[3] have reported studies on a series of eight rabbits given 25 mg. of cortisone per kilogram a day. One rabbit was sacrificed each day over an eight-day period, and the healing rate of experimental femur fractures was observed. Changes consisted chiefly of delayed appearance of granulation tissue and delayed reabsorption of hemorrhage at the site of the fracture. Spain[4] has reported a series of experiments in which twenty mice were given 2 mg. of cortisone a day for five days. The healing process of 0.5 cm. skin wounds was studied, and the chief alteration noted was a delayed appearance of granulation tissue and fibroblasts. Alrich, Carter, and Lehman[5] studied the healing rate of abdominal wounds in rats given cortisone in doses of 6 mg. per day up to twelve days. Tensile strength studies showed a decrease of about 50 per cent in the healing rate as compared to the control wounds. In the animals receiving cortisone, several of the wounds disrupted. Histologic studies of sections showed delayed appearance of granulation tissue. Baxter and associates[6] reported studies on rabbits which showed some delay in appearance of granulation tissue in skin wounds. Cole and associates[7] studied the effect of cortisone in doses of 2 mg. per kilogram per day on the healing of linear aseptic wounds in dogs. No difference in healing was noted between this group and a control group. Paterson and Mitchell[8] found a significant reduction in coronary

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sclerosis in elderly chickens treated with cortisone. Creditor and associates[9] obtained biopsies from wounds in two patients receiving ACTH and demonstrated that, although the wounds were covered with epithelium, there was little proliferation of the fibroblasts in the underlying tissue. Hanlon[10] has reported a patient with a perforated viscus who underwent laparotomy while he was receiving ACTH. The postoperative course was uneventful.

METHODS

Rabbits were used initially as the experimental animal but were abandoned after we found that they tolerated manipulation of the heart and great vessels poorly; then small mongrel dogs were utilized. Cortisone administration was begun three days preoperatively and was continued until the animals were sacrificed. Since vascular anastomoses are usually well healed by the fourteenth postoperative day, it was not felt that it was necessary to pursue the studies beyond this date. Cortisone was given in doses varying from 5 to 25 mg. per kilogram per day. Positive pressure endotracheal ether anesthesia was administered. Thoracotomy was performed through the left fifth intercostal space. The descending aorta immediately distal to the left subclavian artery was mobilized, clamped with noncrushing clamps, divided, and anastomosed with a continuous everting suture of 00000 Deknatel silk. The period of occlusion ranged from eight to fifteen minutes with an average of about ten minutes. The pericardium was then opened and an area of the myocardium of the right ventricle was infiltrated with 1 per cent procaine. A curved noncrushing clamp was applied to the ventricular muscle, after which a 2 cm. incision was made through the entire thickness of the ventricular wall. The incision was closed by 0000 interrupted cotton sutures and the clamp removed. The left auricular appendage was then clamped and the tip amputated. The end of the appendage was closed by a continuous over-and-over suture of 00000 Deknatel silk. The chest wall was closed in layers with cotton.

At autopsy the wounds were examined for gross evidence of healing, infection, hemorrhage, and thrombus formation. The disruptive strength of the aortic and ventricular wounds was studied by applying traction to the wound margins and noting the force in pounds applied at the time of disruption of the wound. The auricular appendage was so friable that the disruptive strength did not seem to be accurately measured by the method we were using.

RESULTS

The animals showed no general effects from the administration of cortisone except that they seemed to be more susceptible to distemper. The operative procedure was well tolerated and recovery was prompt except for a few instances of paralysis of the lower extremities. The development of paraplegia could not always be correlated with the duration of aortic occlusion and occurred in two animals whose aorta was occluded for only ten minutes. Three animals with severe paraplegia died within twenty-four to forty-eight hours after surgery and are not included in these studies. Three with slight paraplegia remained in good health and were sacrificed at the scheduled time. At the time of autopsy,

the thoracotomy wounds uniformly showed gross evidence of normal healing. No hematomas were present, and there was no evidence of wound infection. The pleural cavities were clean and the lungs well expanded. The aortic and ventricular suture lines showed small accumulations of platelet thrombi on the intimal surfaces. The suture line in the left auricular appendage was usually obscured by a small clot.

TABLE I. RIGHT VENTRICLE: DISRUPTIVE STRENGTH IN POUNDS

	DAYS POSTOPERATIVE	NORMAL STRENGTH (IN POUNDS)	STRENGTH OF SUTURE LINE (IN POUNDS)	PER CENT OF NORMAL
Controls	4	1.5	0.5	33
	8	1.25	1.0	80
	8	1.75	1.5	86
	8	1.5	(Broke proximal to suture line)	
Dogs given 5 mg. of cortisone	8	3.5	1.5	43
	3	2.0	1.0	50
	6	1.0	0.75	75
	6	1.5	1.25	83
	9	2.5	1.75	70
	9	1.5	1.0	67
Dogs given 25 mg. of cortisone	10	1.75	1.25	71
	8	1.0	1.5	150
	8	3.0	1.5	50

TABLE II. AORTA: DISRUPTIVE STRENGTH IN POUNDS

	DAYS POSTOPERATIVE	NORMAL STRENGTH (IN POUNDS)	STRENGTH OF SUTURE LINE (IN POUNDS)	PER CENT OF NORMAL	
Controls	4	7.25	3.25	45	
	8	4.0	4.0	100	
	8	9.0	5.5	61	
	8	4.5	5.0	111	
	8	6.5	6.0	92	
Dogs given 5 mg. of cortisone	2	3.75	2.75	73	(Studies 12 hours post mortem)
	3	4.5	3.25	72	
	6	4.5	3.0	67	
	6	4.0	3.5	88	
	9	4.5	(Did not tear at suture line)		
	9	4.5	4.0	89	
	10	4.75	7.75	160	
Dogs given 25 mg. of cortisone	8	4.0	4.0	100	
	8	5.0	4.75	95	

There was no significant difference in the amount of force necessary to pull the suture line apart in the cortisone-treated and control group the same number of days after operation regardless of the amount of cortisone administered (Tables I and II). We did not measure the cross sectional area of tissue at the suture line and thus our determinations were of disruptive strength rather than tensile strength. We also compared the disruptive strength of the suture line to that of a segment of adjacent similar tissue in order that the results might be expressed in percentage of normal (Tables I and II). Again it was

found that there was little difference between the two groups. These measurements are subject to many variations as has been emphasized by Lowenberg and Shumacker.[11] In a few instances the aorta tore where it was grasped by the clamps during the disruptive strength measurement. On such occasions the measurements were repeated.

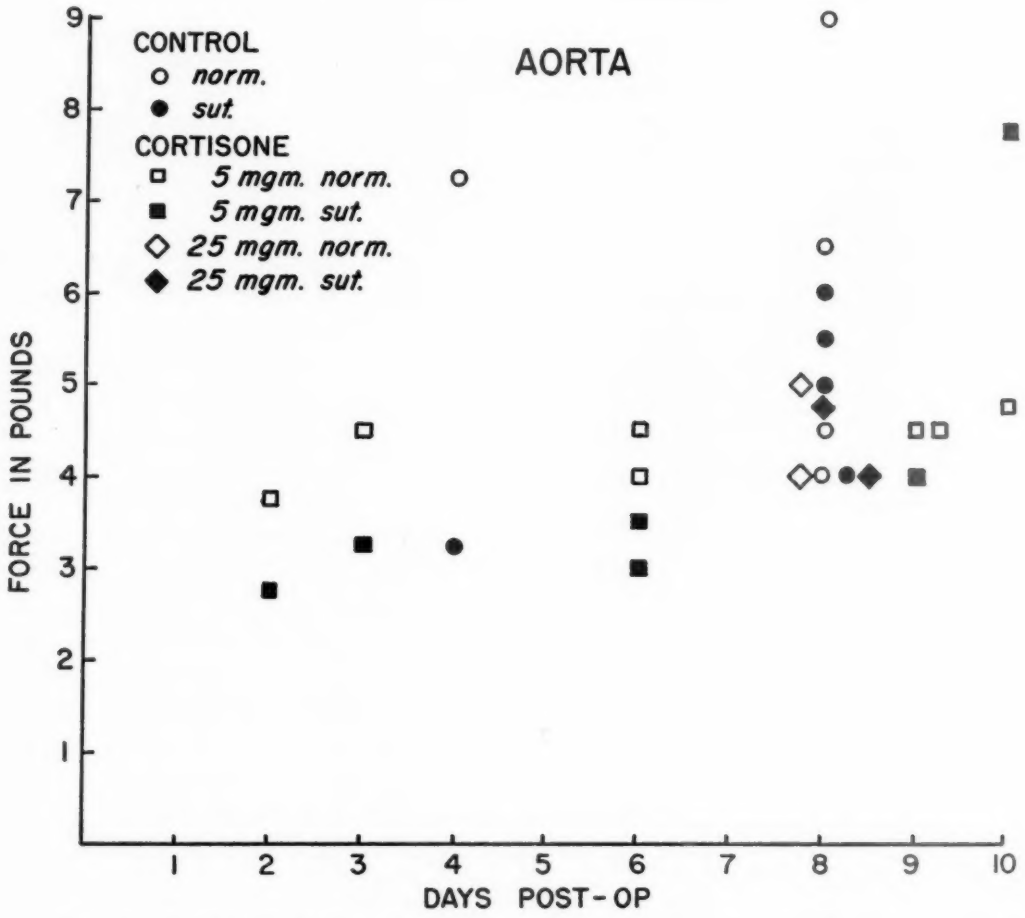

Fig. 1.—Graphic illustration of measurements of disruptive strength of anastomoses and segments of normal aorta in control animals and those given 5 and 25 mg. of cortisone per kilogram.

Sections made through the suture line of each of the specimens were examined histologically. Hematoxylin and eosin stains and van Gieson's stains for collagen and elastic tissue were prepared. In all instances tissue sections from control animals could not be distinguished from tissue sections of animals treated with cortisone, regardless of the amount of cortisone given. Specimens included sections from the ventricle, auricle, and aorta of both treated and control animals. The findings were as follows:

Hematoxylin and Eosin Stains.—In the specimens from the auricle and ventricle of dogs sacrificed on the fourth postoperative day, the findings were similar. Moderate edema and some necrotic fibers associated with leukocytic

infiltration were found. In a few areas the myocardium appeared to be replaced by fibrin in which a few fibroblasts could be seen. A layer of fibrin was present on the epicardial surface and fresh thrombus formation was present on the endocardial surface. The specimens from these tissues in the dogs sacrificed on the eighth postoperative day showed only slight swelling and no necrosis about the suture line. Areas about the individual sutures were filled with young fibroblasts, very little collagen was present, and only a few areas showed infiltration by lymphocytes.

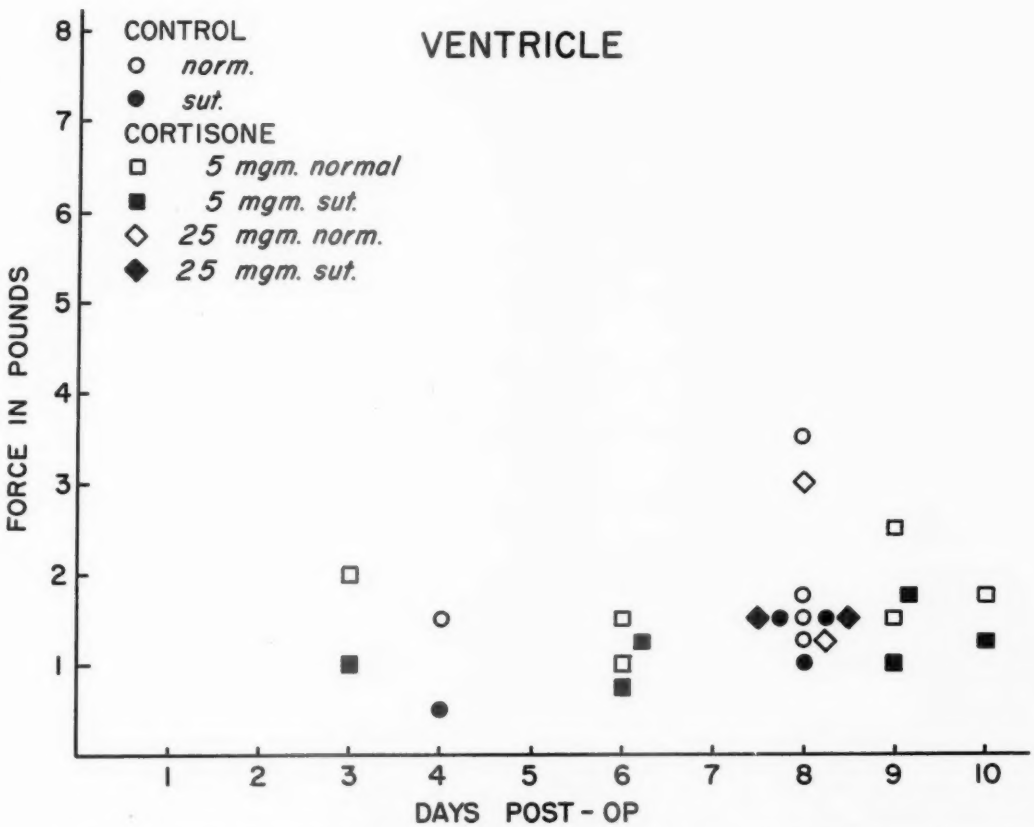

Fig. 2.—Graphic illustration of measurements of disruptive strength of ventricular wounds and segments of normal ventricle in control animals and those given 5 and 25 mg. of cortisone per kilogram.

In the specimens of aorta from animals sacrificed on the fourth postoperative day, there was much swelling of the media and considerable necrosis in the region of the incision. Many pyknotic nuclei were present. The adventitia was thickened by a mass of fibrin containing degenerating red cells and leukocytes. The intima was edematous and elastic fibers were indistinct. In the specimens of aorta from the animals sacrificed eight days after operation, the intima was still edematous and the elastic fibers indistinct in the region of the incision. The media was diminished in thickness, but in some portions was still edematous and contained occasional pyknotic nuclei. The adjacent adventitia was thick-

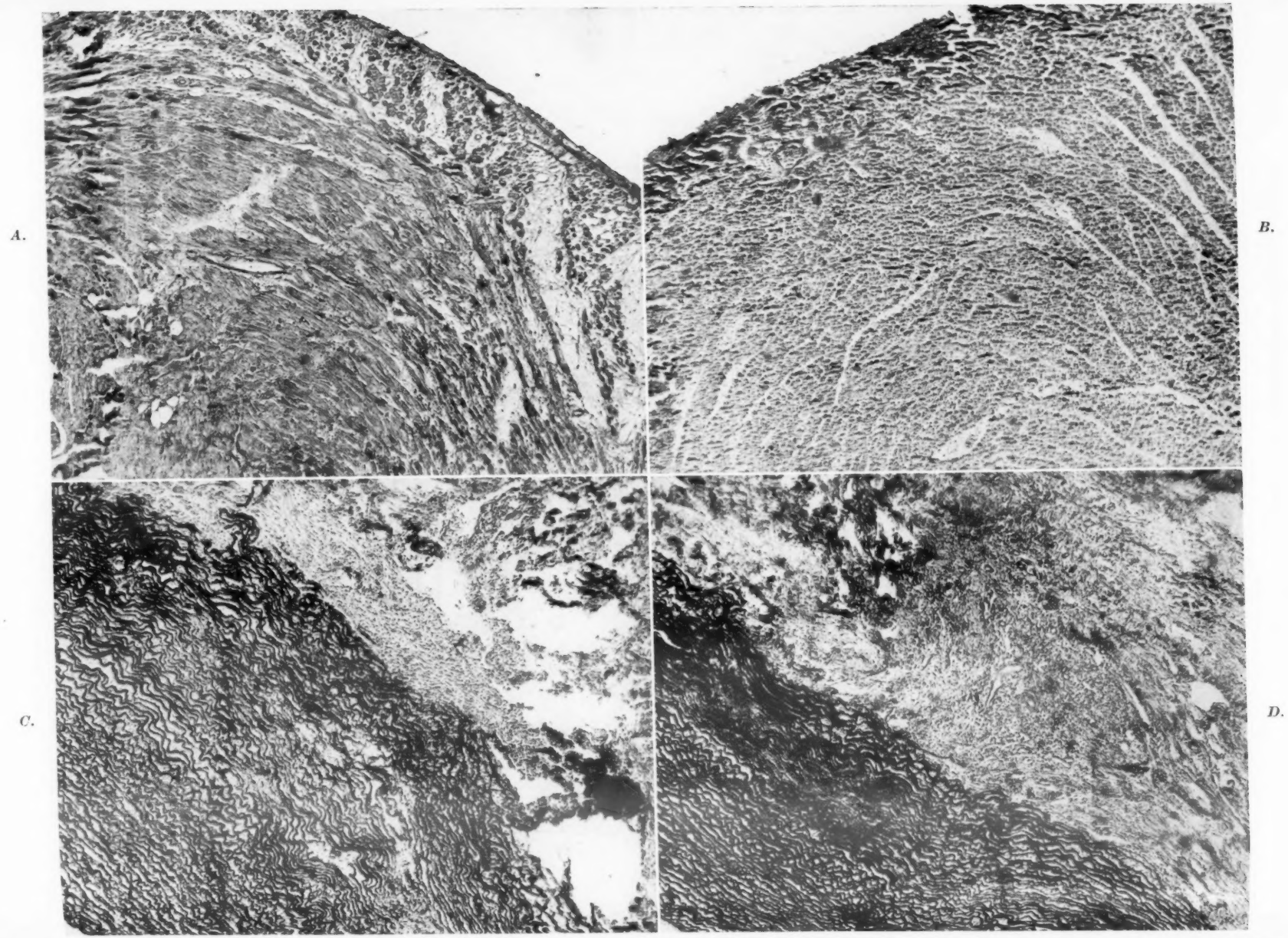

FIG. 3. (For legend see opposite page.)

ened by organizing granulation tissue which was diffusely infiltrated by lymphocytes.

Van Gieson's Stains.—In the ventricle and auricle of the dogs sacrificed four days after operation, some irregular deposition of collagen and a moderate amount of granulation tissue was present about the line of the incision. In the animals sacrificed eight days after operation, the specimens from these vessels showed a chronic inflammatory reaction about the suture line. There was a slight increase in collagen over the adventitial surface (Fig. 3, *A* and *B*).

The aorta of the dogs sacrificed on the fourth postoperative day showed slight necrosis and some inflammatory reaction about the line of the incision. No collagen fibers could be seen. The specimens of this vessel from the animals sacrificed eight days after operation showed moderate inflammatory reaction near the incision and early granulation tissue formation (Fig. 3, *C* and *D*). There was a slight increase in collagen over the adventitial surface, but none was present in the line of incision. Healing was moderately well advanced.

Thus normal healing was present histologically in all of these wounds regardless of whether cortisone was administered or not.

DISCUSSION

This experiment was not designed to show detailed variations in wound healing. There is, however, a constant relationship between the cortisone-treated and control animals, and the studies of disruptive strength and histologic changes indicate no effect of cortisone on the healing of wounds of the cardiovascular system.

One of the greatest considerations in this experiment was the determination of the proper dose of cortisone for dogs, because most previous investigation had been carried out on rabbits, rats, and mice. There is a considerable variation in the dose required by different species. Rabbits show a greater response to cortisone than do rats and mice. The eosinophil response was not considered reliable as an index for cortisone effect, because the normal eosinophil count in the dog is so inconstant.[12] We wanted to be sure that an excess amount of cortisone was present in addition to that necessary to compensate for adrenal depression. For this reason we increased the dose to 15 and finally 25 mg. per kilogram. As compared to known adequate doses in other experimental animals and patients, 25 mg. per kilogram seemed to be an extremely large dose.

We are unable to explain why there was no inhibition of wound healing in the animals receiving cortisone. The disruptive strength studies might not have been sensitive enough to demonstrate a difference in wound strength. In wounds two to four days old, one is actually measuring the force necessary to cause the sutures to pull through the sutured tissue. Even so, one would expect

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Fig. 3.—Photomicrograph (×75) of tissue adjacent to healing wounds.

A, Section of ventricle from control dog sacrificed four days after operation.

B, Section of ventricle from dog given 15 mg. of cortisone per kilogram daily for three days before operation and until he was sacrificed four days after operation.

C, Section of aorta from control dog sacrificed eight days after operation.

D, Section of aorta from dog given 25 mg. of cortisone per kilogram daily for three days before operation and until he was sacrificed eight days after operation.

that if diminished collagen deposition and fibroblastic response were present along the suture line in the cortisone-treated animals, less force would be necessary to pull out the sutures in this group than in the control animals. In wounds eight to nine days old which are strengthened by the normal healing processes, one would again expect to see a lower disruptive strength if these processes had been retarded by the administration of cortisone. Also, if fibroblastic response and collagen deposition had been retarded, one would expect it to be demonstrated in the histologic studies. One consideration as to why previously reported similar studies of wound healing in skin and subcutaneous tissue differ from those presented here might be the difference in blood supply to these tissues. The intimate blood supply of vascular structures might have some effect on the healing processes.

While one cannot draw definite conclusions which might be applied to patients from these studies, it seems likely that operations may be performed on the vascular system of patients receiving cortisone with no greater risk of vascular wound disruption than in similar patients not receiving this drug.

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Case Reports

PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE

A Case Report

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PROGRESSIVE bacterial synergistic gangrene is an unusual ulcerative process of the skin which, as a rule, occurs in postoperative wounds, but not necessarily so. It is believed to be a fairly definite clinical entity at the present time. Cullen,[1] in 1924, was probably the first to describe the condition. Brewer and Meleney demonstrated to their satisfaction by careful investigation that the etiologic agents were a microaerophilic nonhemolytic Streptococcus and a *Staphylococcus aureus.* These two organisms existed in a state of symbiosis to produce the gangrenous ulceration of the skin that is seen in this disease. Their first case, which was reported in 1926,[2] was that of ulceration which developed in the abdominal wall following drainage of an appendiceal abscess. They were able to reproduce the lesion in guinea pigs by subcutaneous injection of the combination of the microaerophilic nonhemolytic Streptococcus and the *Staph. aureus,* but not by injection of either organism alone. This work has been confirmed by others.

This condition is sometimes referred to as Meleney's disease or Meleney's ulcer. We have recently had experience with a case which presented many problems and unusual features. It illustrates the fact that when the proper diagnosis is not made promptly and adequate therapy given, the patient may slip into serious condition before one realizes it. Heroic measures may then be required to save life. This case is also interesting because of the extent and distribution of lesions.

C. H., a 53-year-old white man, a baker by trade, was admitted to the Dermatology Service of Hines Veterans Hospital on June 1, 1950, with the complaint of a "sore" on the inner aspect of the right thigh of two and one-half months' duration. The patient stated that originally he noted a small pimplelike lesion on the inner aspect of the right thigh which he squeezed. He then noted that an ulcer developed which gradually enlarged. He treated this himself with boric acid compresses and various ointments. After one week he consulted a private physician who treated him with four x-ray exposures over a three-week period. There was no improvement; in fact, the ulcer continued to enlarge. Three weeks prior to admission he was given five injections of penicillin and was also given Chloromycetin, 250 mg. three times a day, for ten days. There was still no improvement and on admission the ulcer was as shown in Fig. 1.

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The past history was nonrevealing. He had been in good health all of his life. Systemic review was also irrelevant. Physical examination revealed a 53-year-old, fairly well-nourished man whose height was 5 feet 8 inches, and whose weight was 140 pounds, which was his average weight. He was in considerable distress because of the painful ulcer of the right thigh. There were scattered small tumors on the right forearm, upper arms, and left thigh which were soft and freely movable, and which were thought to be multiple lipomas. The remainder of the examination was entirely normal except for the right thigh. There was a large, ulcerated area on the right thigh, extending well onto the anterior and posterior surfaces. There was some healing with marked peripheral extension of a raised, gangrenous border about one inch in thickness. This border was undermined and surrounding it was an area of erythema two inches in width. The exudate, readily obtainable from beneath the gangrenous crust, was sanguinous and foul smelling.

Fig. 1.—Appearance of the initial ulcer on admission. Note the gangrenous border.

Admission laboratory data revealed negative serology. The urinalysis was reported as negative. The admission white blood count was 8,500; the red blood count 4,890,000, and the hemoglobin was 14.5 Gm. A chest x-ray film and a barium enema were negative. During his long stay in the hospital many cultures were taken. The initial culture revealed hemolytic *Staph. aureus*, genus Hemophilus and paracolon Bacilli. No attempt was made initially to recover anaerobic organisms. Fungus studies were made which were nonrevealing. The organism of blastomycosis was especially looked for but never found.

The case proved to be a diagnostic problem from the start. The initial impression was granuloma of unknown etiology—possibly one of the fungus group. Repeated biopsies showed only chronic granulation tissue and epitheliomatous hyperplasia. There was never any biopsy evidence of malignancy.

The patient was tried on tyrothricin compresses initially and after a brief period it was obvious that the ulcer was enlarging rapidly. Many other drugs were used, including penicillin, streptomycin, Chloromycetin, Aureomycin, bacitracin, sulfadiazine, Vioform, and bismuth subsalicylate, as well as protein supplements, multivitamins, and other supportive measures. He also received potassium iodide, two courses of ACTH, and x-ray therapy (900R) without success.

On July 14, 1950, a small pustule was noted on the little finger of the left hand (Fig. 2) and shortly thereafter, three separate lesions appeared on the left lower extremity. These rapidly developed into typical gangrenous ulcers. The appearance of the patient on Aug. 3, 1950, is shown in Fig. 3, on Aug. 23, 1950, in Fig. 4, and on Sept. 18, 1950, in Fig. 5. It will be noted that all of the lesions were rapidly enlarging, but some showed central healing.

The diagnosis remained in doubt. The patient's general condition became poor, his weight fell to 85 pounds, and he required repeated blood transfusions. On Nov. 24, 1950, he was seen by the Plastic Surgery Department. It was felt that the process was one of progressive bacterial synergistic gangrene as originally described by Cullen.[1] At this time the process had extended to include most of both lower legs and two areas on the left forearm. Though it seemed that the patient's only opportunity for cure lay in surgical excision and skin grafting, it was felt that in view of the extensive involvement a small area should be tried first. Two of the new lesions on the forearm were excised well beyond the area of erythema and an immediate skin graft was applied. The operative procedure was carried out on Dec. 4, 1950, and resulted in complete take of the grafts and healing of the areas. Subsequently, all the other ulcerating areas were excised and debrided. On Dec. 29, 1950, five large sheets of skin were taken from the patient's chest and applied to both lower extremities. His appearance before grafting is shown in Fig. 6.

Fig. 2.—A typical ulcer appeared on the little finger of the left hand, Aug. 3, 1950.

On Jan. 18, 1951, postage stamp grafts were applied to some raw areas which were still present on the left hip and left leg and on Feb. 26, 1951, further grafting was done to several small open surfaces on both lower extremities. These grafts took satisfactorily and by now both legs were fairly well covered. His condition, which had been extremely poor, began to improve rapidly thereafter. Whereas he had run a fever of between 100° and 102° F. for several months, his temperature now returned to normal. On March 8, 1951, he developed an episode of jaundice, fever, and malaise which was undoubtedly an homologous serum jaundice. He slowly recovered and by April, 1951, he was up walking about the wards. However, in August, he developed another ulcer on the left ankle which began rapidly to enlarge (Fig. 7). This ulcer was treated with bacitracin solution injected around the margin of the lesion with some improvement, but this also eventually required excision and grafting.

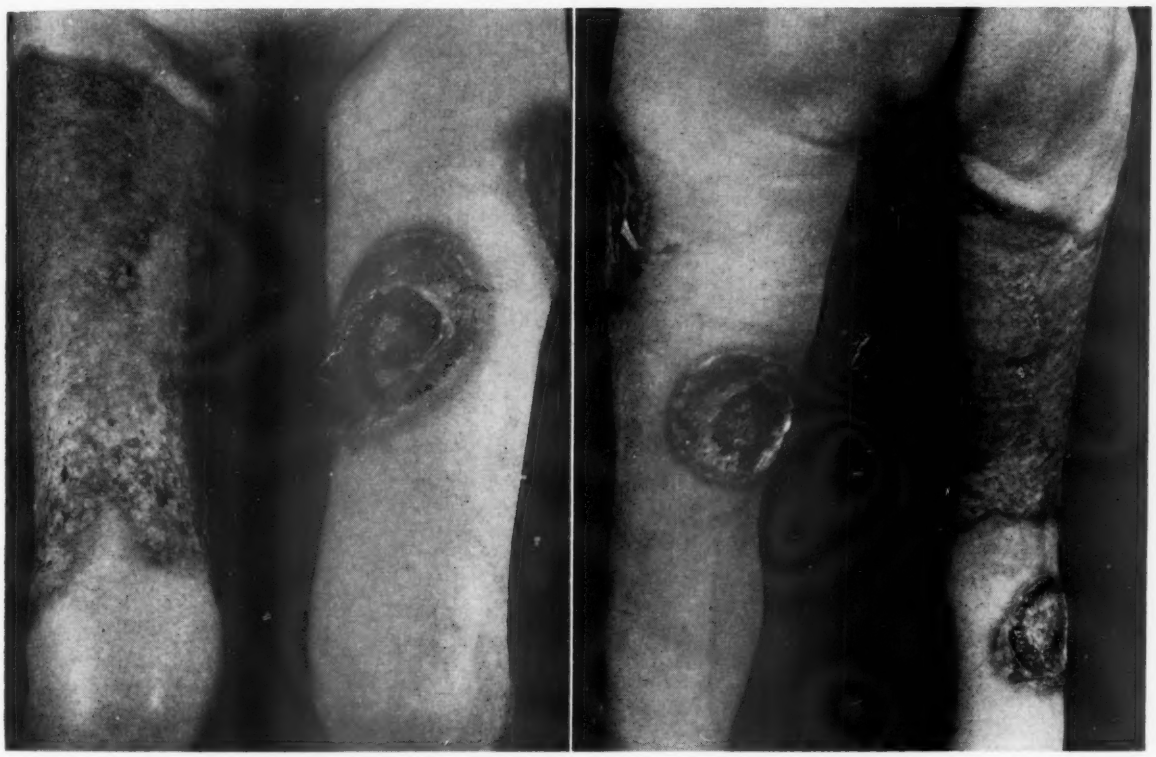
On Sept. 8, 1951, while changing the dressing on a donor site on the left anterior chest, a small furuncle-like lesion was noted underneath the tape. This broke down and shortly thereafter developed into a typical gangrenous ulcer which again rapidly enlarged. On Sept. 17, 1951, this was excised and grafted successfully. Anaerobic cultures from the

A. *B.* *C.*

Fig. 3.—Aug. 3, 1950 (two months after admission). Note the appearance of three new ulcerations. The original lesion involves practically the entire right thigh, but shows some tendency to heal centrally.

depths of this excised lesion on the chest revealed microaerophilic nonhemolytic Streptococcus and *Staph. aureus*. It should be mentioned that although *Staph. aureus* had been recovered on many previous occasions from other ulcers, the microaerophilic Streptococcus had not been recovered previously. This is presumably due to the lack of an adequate bacteriologic setup for recovering microaerophilic and anaerobic organisms.

By October, 1951, the patient was well enough to return home. Fig. 8 shows photographs taken just prior to discharge.



A. *B.*

Fig. 4.—Aug. 23, 1950. Note the progression in a matter of three weeks despite large doses of antibiotics.

COMMENT

Meleney[3] classified infectious gangrene of the skin as follows:

Acute.—

1. Gas gangrene
2. Hemolytic Streptococcus gangrene
3. Erysipelas

Chronic.—

1. Progressive bacterial synergistic gangrene
2. Gangrenous impetigo (ecthyma)
3. Fusospirochetal gangrene
4. Amoebic gangrene of skin

The differential diagnosis here rested among the chronic types. This case had much in common with the picture of gangrenous impetigo (ecthyma). However, this condition (which is thought by some authorities to be simply a more

A.

B.

C.

Fig. 5.—Sept. 18, 1950. Further rapid progression can be seen. The patient's general condition was becoming poor.

severe form of impetigo contagiosum) is usually seen in debilitated individuals with recurrent attacks of diarrhea or colitis which were not present in our patient. The lesions of gangrenous impetigo are multiple and may coalesce, but seldom are more than 1 or 2 cm. in diameter. Further, it should be noted that there was no evidence that our patient had a contagious disease. He was not isolated and no other cases developed either among the other ward patients, or among members of his family.

Fig. 6.—Dec. 21, 1950. By now both lower extremities had become entirely involved except the feet. Grafting was begun shortly after this photograph was taken.

Fusospirochetal gangrene develops as a result of human bites. There was no history of bite.

Amoebic gangrene was considered. However, amoebae were never found, although attempts were made to find them.

Although most instances of progressive bacterial synergistic gangrene have occurred at the site of postoperative wounds, this synergism or symbiosis may originate from a variety of infectious processes of the skin. This patient's initial lesion was a small furuncle which he squeezed and possibly inoculated

with an additional organism. This additional organism, plus the agent responsible for the furuncle, conceivably flourished in a symbiotic manner to cause the whole process. Similar cases have been reported.[4, 5]

The tendency to develop multiple sites of ulceration is rare. Meleney reported one such case in 1945.[5] His patient had a total of twelve gangrenous ulcers—one on the right leg, one on the left thigh, one over the right hip, six on the anterior part of the chest, and three on the inner surface of the right arm. The initial lesion in his patient was a boil on the right leg, and in this respect his case is strikingly similar to the case under discussion here.

Fig. 7.—Aug. 8, 1951. Note grafted areas of left lower leg, but a new ulcer has started at the ankle.

DISCUSSION

Great confusion has persisted through the years as to the bacteriology of this disease. Although Meleney has insisted that the microaerophilic nonhemolytic Streptococcus and the *Staph. aureus* are specific, others have reported a wide variety of organisms.[4, 6] This question still does not seem to be settled at the present time. Churchill in discussing Holman's paper stated: "There is real difficulty ahead in attempting to assign a specific etiological agent to as variable and protean a disease as chronic progressive superficial ulceration." He further stated: ". . . fortunately the proper treatment may be carried out irrespective of these uncertainties as to etiology." The treatment he recommended in 1935 was excision of the margin of the ulcer with electrocautery knife, followed by skin grafting. Radical treatment by excision became popular as the most effective method. However, with the advent of antibiotics, many successful results were reported with the use of these agents—particularly penicillin and bacitracin.[5, 7]

It was our experience in this case that aside from radical excision, bacitracin was the only drug that had any effect whatsoever. It was felt that bacitracin, used locally, seemed to slow down the spread, but even so, those ulcerations which were so treated eventually required excision and grafting.

It is important to emphasize that although it is highly desirable to obtain an accurate bacteriologic picture with sensitivity tests, one should not delay radical treatment for that purpose. The patient may progress rapidly downhill, become thoroughly demoralized and dangerously ill from the effects of anemia, hypoproteinemia, and toxicity. Fatalities have also been reported as a result of erosion and hemorrhage from major blood vessels.[4] It is felt that this case would have had a fatal outcome had not surgical intervention taken place.

Fig. 8.—Nov. 8, 1951. Appearance shortly after discharge. All lesions are well healed except for some crusting. Patient's general condition is excellent.

SUMMARY

1. A case of progressive bacterial synergistic gangrene is reported which was unusual because of the mode of onset from a furuncle on the thigh, and because of the multiplicity of the ulcerations.

2. It demonstrated a complete lack of response to antibiotics with the possible exception of bacitracin used locally.

3. We feel that surgical treatment by excision and skin grafting should not be long delayed, when it becomes obvious that antibiotic and other conservative therapy is inadequate.

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RUPTURE OF THE ESOPHAGUS BY COMPRESSED AIR

Case Report

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COMPRESSED air is a rare cause of rupture of the esophagus, although it has produced rupture of the colon not infrequently.[1] These accidents commonly have occurred in factories where compressed air hoses are employed. Petren[2] in 1908 reported the case of a 27-year-old factory worker who stumbled while carrying a compressed air hose in his mouth. Air under a pressure of seven atomospheres was released directly into the mouth. The patient died twenty-seven hours later and was found at post-mortem examination to have a rent in the esophagus 6 cm. in length extending inferiorly from a point 1.5 cm. below the birfurcation of the trachea. The rent involved the left posterolateral wall of the esophagus. There was a left pyopneumothorax together with marked mediastinal and subcutaneous emphysema. The present case is a second example of rupture of the esophagus by compressed air under most unusual circumstances.

Several investigators have studied the force necessary to produce rupture of the esophagus. MacKenzie[3] in 1884 employed fresh cadaver material and found that an average hydrostatic pressure of five to ten pounds per square inch produced a longitudinal rent in the lower one-third of the esophagus, whether the pressure was applied at the proximal or distal end of the esophagus. In 1948 Kinsella, Russell, and Hertzog[4] carried out similar experiments by distending the esophagus of fresh cadavers with air. Rupture of the esophagus occurred at pressures varying from 1.9 to 6.3 pounds per square inch. The lower one-third of the esophagus was found to be the most vulnerable portion. This area has also been involved most frequently in postemetic or so-called "spontaneous rupture" of the esophagus.

CASE REPORT

History.—L. R. (UH No. 690803), a 3-year-old white boy, was admitted to the Thoracic Surgery Service of the University Hospital at 5:30 P.M. on Sept. 30, 1950. Three hours before admission he had been playing beside a homemade tractor in a yard near his home. There was a loud report, and he ran crying into the house. The patient was coughing and blood was present in the mouth. Swelling was noted almost immediately about the neck and shoulders. This later involved the left side of the face and the left eyelids. There was progressive dyspnea. The patient was rushed to his personal physician who made two small stab wounds in the tense neck and referred the patient to the University Hospital.

As the accident was reconstructed later, the patient had bitten the inner tube of one of the tractor tires which had a large cut in the casing. The inner tube blew out and the full

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force of the compressed air within it was released into his mouth (Fig. 1). The air pressure within the inner tube was estimated to be between twenty-five and thirty pounds per square inch.

Physical Examination.—The temperature was 102° F. rectally; blood pressure, 84/60; pulse, 112; respirations, 32 (labored).

The patient was acutely ill and was dyspneic. There was marked subcutaneous emphysema involving the shoulders, neck, and face. The left eye was completely closed. The mouth, pharynx, ears, and nose were normal. No lacerations of the mucous membranes were seen. There were two tiny stab wounds in the anterior neck. These contained rubber wicks. The trachea and mediastinum were displaced markedly to the right. Tactile fremitus and breath sounds were absent over the left side of the chest. The pulse was regular but weak. The tympanitic abdomen was not tender. Bowel sounds were heard on auscultation of the abdomen.

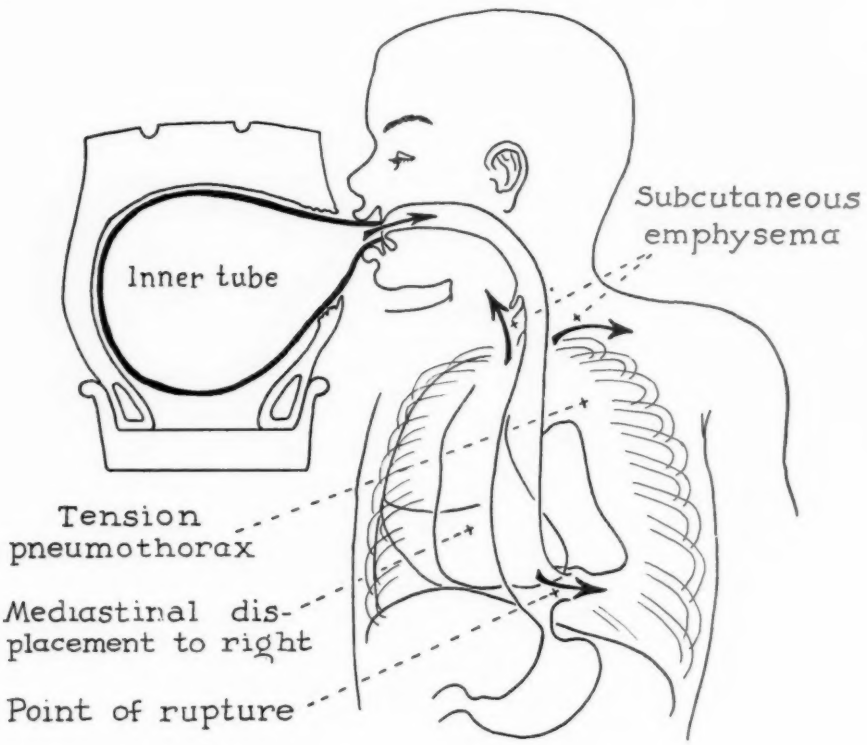

Fig. 1.—Diagram illustrating mechanism of accident.

Laboratory Data.—Hemoglobin was 15 Gm.; W.B.C. was 7,500; the urine contained one plus sugar.

Roentgenograms.—Examination of the chest showed an almost total collapse of the left lung and mediastinal shift to the right (Fig. 2). There was marked mediastinal and subcutaneous emphysema. No air was present in the peritoneal cavity.

Course.—Although the mechanism of the accident was not known at this time, immediate decompression of the patient's tension pneumothorax was imperative. Under local anesthesia an intercostal tube was inserted in the second left interspace anteriorly. The dyspnea was relieved. The tube was connected to water seal drainage and it was noted that material resembling stomach contents appeared in the drainage bottle. A Lipiodol swallow demonstrated a posterior perforation in the lower one-third of the esophagus approximately 6 cm. above the gastric cardia, the oil escaping into the left pleural cavity.

The patient's general condition was poor, despite his relief from respiratory distress. It was felt that open thoracotomy and suture of the esophageal perforation would be accompanied by serious risk. Dependent, airtight drainage of the left chest was carried out following resection of a segment of the tenth rib in the posterior axillary line under local anesthesia. This drainage tube was connected to a water seal bottle. Suction was applied to both intrapleural tubes. The left lung expanded rapidly and the anterior intercostal tube was removed five days after admission.

The patient received intramuscularly 100,000 units of aqueous penicillin every three hours and 0.5 Gm. of streptomycin twice daily. Small amounts of sterile fluid were allowed by mouth. These drained, for the most part, through the pleural cavity and into the drainage bottle. Fluid balance was maintained for seventy-two hours by means of intravenous glucose and saline. At this time a Levine tube was passed into the stomach for feeding purposes. It was tolerated poorly and was subsequently removed. Sixteen days following admission a feeding gastrostomy was carried out.

Fig. 2.—Admission roentgenogram showing left tension pneumothorax and marked mediastinal and subcutaneous emphysema.

There were daily temperature elevations to 102° F. rectally for eighteen days; the patient's fever then slowly subsided. Roentgenograms demonstrated a mediastinal abscess which was draining poorly into the left pleural cavity. The abscess closed spontaneously as plans were being made to drain it by posterior mediastinotomy. Drainage of the gastric contents and saliva into the left chest gradually ceased and the empyema drainage tube was removed forty days after admission. Seven days later the gastrostomy tube was removed and the patient was able to take a full diet by mouth. He was afebrile and had shown a five pound weight gain.

A barium examination of the esophagus was made one month following admission. This demonstrated no communication with the pleural space but did show a small sinus track extending into the mediastinum. No additional examinations were made since the patient had had already a considerable amount of exposure to radiation.

The patient was discharged on Nov. 19, 1950. When last seen eight weeks after discharge, he appeared to be perfectly well. In April, 1952, the patient's parents stated that his development was normal and that he had no symptoms referable to his chest or esophagus.

DISCUSSION

The primary therapeutic consideration when the patient was first seen was decompression of the left tension pneumothorax. Only after this had been done was an esophageal rupture recognized. It would have been desirable to perform a prompt thoracotomy and to close the esophagus as has been recommended.[5, 6] The poor condition of the patient, however, made such a course of action unwise. As a compromise, dependent drainage of the left chest was instituted, in addition to the decompressing drainage that had been carried out in the second anterior intercostal space.

The patient's course was marked by fever and by the presence of a poorly drained mediastinal abscess which finally closed spontaneously. Gastrostomy was necessary for feeding purposes.

Recovery was favorably influenced by the absence of the gross mediastinal soiling with gastric contents which are spread throughout the mediastinum in postemetic rupture of the esophagus. It is of considerable interest that the rupture occurred in an area similar to that seen in postemetic rupture of the esophagus.

SUMMARY

An unusual case of rupture of the esophagus in a 3-year-old boy is reported. The accident occurred when the patient bit an inner tube bulging through a tractor tire casing. Recovery followed superior and inferior drainage of the left pleural cavity and a feeding gastrostomy.

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THE COEXISTENCE OF DUODENAL ULCER AND GASTRIC CARCINOMA

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ONE of the generally accepted clinical axioms is that carcinoma of the stomach does not develop in patients with a duodenal ulcer. This is substantiated by the few reports of this association, ninety-eight such cases being recorded in the past thirty years.[1-3, 6-10] The relative rarity of coexistence of the two lesions may lead to complacency regarding the nature of a gastric ulcer when a duodenal ulcer is simultaneously demonstrated. The purpose of this paper is to describe the finding of an early gastric carcinoma in a patient operated upon for duodenal ulcer and to emphasize the possible coexistence of these two lesions.

CASE REPORT

P. G. (No. 2912), a 46-year-old retired Army Sergeant, was admitted to the Brooklyn Veterans Administration Hospital on Oct. 10, 1950, with the chief complaint of epigastric pain.

Present Illness.—The patient first noted the onset of epigastric pain in 1941. This pain was most marked before meals, was relieved by food and antacids, and was frequently accompanied by nausea and vomiting. He was admitted to the station hospital, where a duodenal ulcer was demonstrated on x-ray. After several weeks of medical treatment, he was returned to active duty, free of symptoms. The patient noted the gradual return of the pain and despite milk and cream feedings was again hospitalized in 1943, when gastrointestinal series again showed a duodenal ulcer. This intermittently severe symptomatology continued and required hospitalization again in 1945, while the patient was in the Army, and again in 1947, two years following his discharge. On all these occasions a duodenal ulcer was demonstrated and temporary remissions were obtained by medical treatment. In January of 1950 the patient again noted the return of epigastric pain. However, on this occasion, despite prolonged dietary treatment, the pain seemed more persistent and was described as "always being with me." After months of ambulatory treatment without relief, he finally sought hospitalization.

Physical Examination.—On admission, examination was noncontributory except for tenderness on deep palpation in the epigastrium and left upper quadrant of the abdomen.

Course in the Hospital.—Gastrointestinal series demonstrated generalized coarsening of the mucosal folds of the stomach, but no filling defect was noted. The duodenal bulb showed a persistent organic deformity but no ulcer niche (Fig. 1). Gastric analysis on two different occasions showed free hydrochloric acid with a high of eighty units and one hundred twenty units, respectively. The patient was placed on a bland diet, sedation, and milk and cream feedings between meals. Despite treatment, he continued to have intractable

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pain and was transferred to the Surgical Service for gastric resection. At operation, on Jan. 12, 1951, the first part of the duodenum presented scarring of the anterior wall with secondary pseudodiverticulum formation. On the greater curvature of the stomach, in the mid-portion, a firm mass, 2 cm. in diameter, was palpated. The overlying serosa appeared normal and no lymphadenopathy could be demonstrated. The stomach was opened and an ulceration, measuring 1 cm. in diameter and surrounded by a firm, elevated margin suggestive of carcinoma, was found. Because of this, a radical subtotal resection of the stomach with total removal of the omentum was performed. The patient had an uneventful postoperative course and was discharged on the twelfth day after operation. The pathologic report was: (1) carcinoma of the stomach (Figs. 2*A* and 2*B*), and (2) peptic ulcer of the duodenum.

The patient was seen two years after operation, showed no evidence of metastasis, and was completely free of his previous symptoms. Gastric analysis showed no free hydrochloric acid and gastrointestinal series revealed a well-functioning stoma.

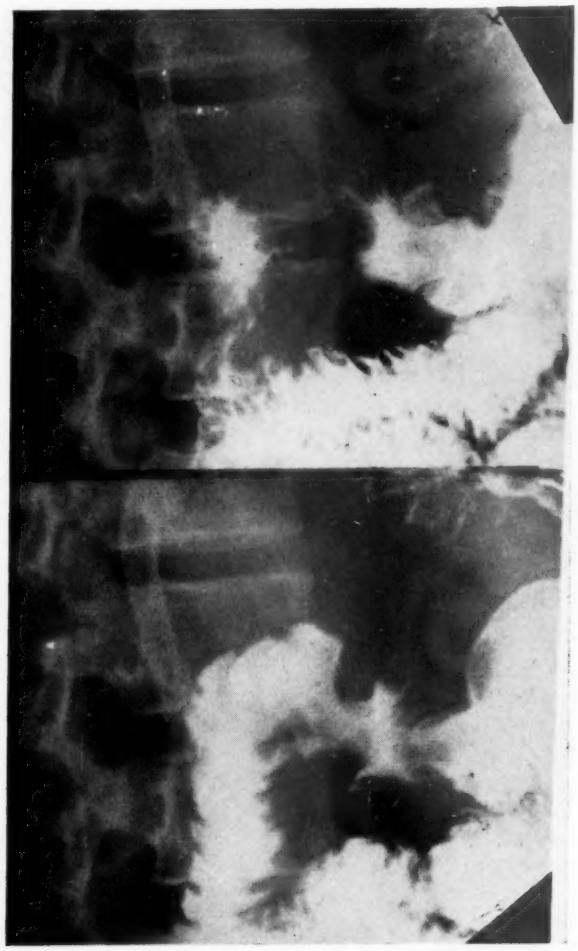

Fig. 1.—Spot film of duodenum revealing persistent organic deformity of the first portion of the duodenum.

COMMENT

The occurrence of gastric carcinoma in patients with duodenal ulcer is a difficult problem to assay.[1-10] The most comprehensive article is from the Mayo Clinic[1] where only forty-eight cases of gastric carcinoma were found among

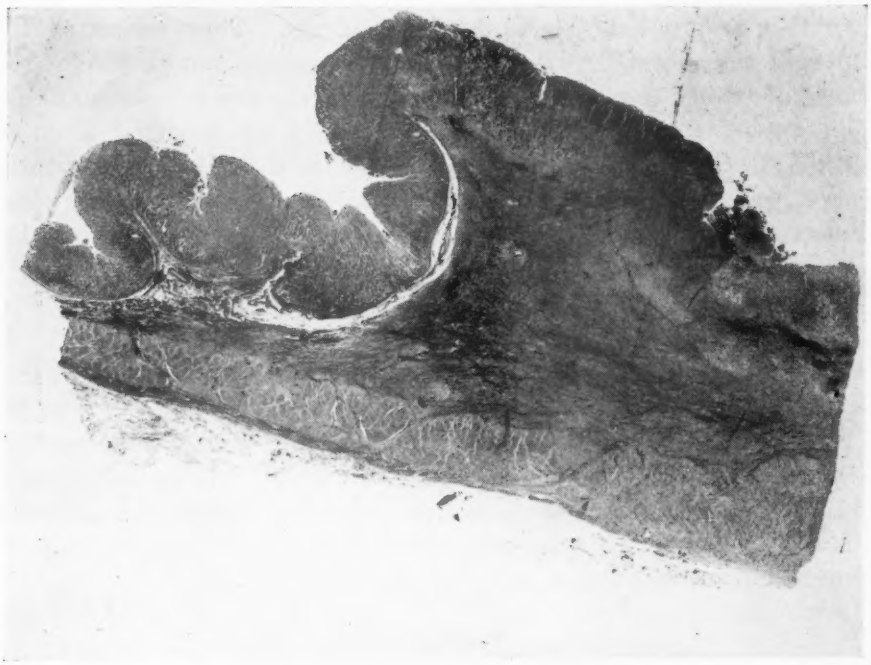

Fig. 2*A*.—Photomicrograph of the stomach wall showing an irregular deep-seated ulcer at the site of the carcinoma.

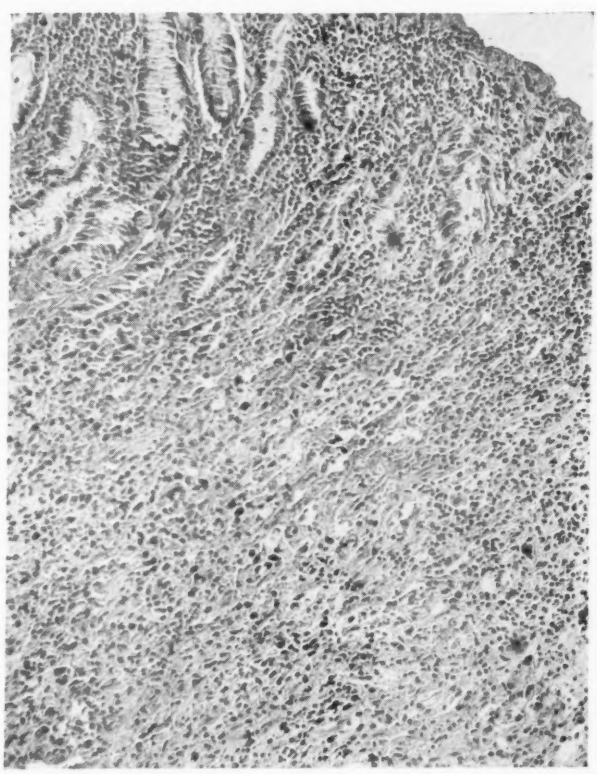

Fig. 2*B*.—Photomicrograph of the lateral wall of the ulcer showing malignant cells extending laterally toward the mucous membrane. Magnification ×100.

forty-five thousand patients with duodenal ulcers. They estimated the concomitant occurrence of the two diseases in the general population to be about 0.01 per cent. Since the incidence of gastric carcinoma as a cause of death is about 3 per cent, it would appear that patients with duodenal ulcer are less prone to the development of cancer of the stomach than those without duodenal ulcer. We feel that this is a valid conclusion, but should not carry with it the dangerous corollary that a gastric ulcer when demonstrated with a duodenal ulcer is necessarily of a benign nature.

CONCLUSIONS

1. A case of carcinoma of the stomach found in a patient with a duodenal ulcer is reported. Only ninety-eight such cases have been found in the literature.

2. We believe that the presence of a duodenal ulcer should not influence the treatment of a coexisting gastric ulcer.

3. In the patient reported there was a definite change of symptomatology which might have been interpreted as indicating the presence of a new lesion superimposed on an old duodenal ulcer.

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EXCISION OF CONGENITAL DIAPHRAGM OF THE JEJUNUM WITH REPORT OF A SUCCESSFUL CASE

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INTRODUCTION

COMPLETE congenital intrinsic obstruction of the intestines may be classified into two groups: In the first, an internal septum or diaphragm occludes the lumen without break in the continuity of the bowel; in the second, the dilated proximal segment ends in a blind sac, separated from the distal collapsed bowel or connected by a thin, fibrous cord.

The incidence of atresia of the jejunum, as compared to other areas of the intestine, varies from 4 per cent (Glover and Barry[1]) to 14.9 per cent (Davis and Poynter[2]), with the first type less common than the second. Krieg[3] reviewed 245 cases of atresia of the duodenum, of which only four, or 1.6 per cent, were congenital diaphragms. The latter are found more frequently in the duodenum than elsewhere, and it is possible that many are not so classified because they are treated by short-circuiting anastomosis, following incomplete exploration and diagnosis. Only an occasional case of complete diaphragm of the jejunum has been noted in the literature, with no reported survivals.

CASE REPORT

Baby F., a white male infant, weighing five pounds nine and one-half ounces, was born seven weeks prematurely at Emory University Hospital, Sept. 18, 1950. He was delivered spontaneously after an uncomplicated pregnancy and labor, cried at once, and had no respiratory difficulties. Immediate examination disclosed a slight tongue-tie, a small papilloma on the right ear lobe, and maldevelopment of the intrinsic muscles of both thumbs so that they remained adducted. No other anomalies were noted. The child was given routine premature care.

Fourteen hours after birth the infant began to vomit greenish fluid at three to four hour intervals. A roentgenogram (flat plate) of the abdomen twenty-four hours after birth revealed a small amount of air in the stomach, with no appreciable amount in the remaining gastrointestinal tract (Fig. 1).

At twenty-nine hours of age the child was referred by Dr. J. Harry Lange for surgical consultation. Except for slight distention in the epigastrium, the entire abdomen was markedly flat. There were no palpable masses and no audible peristalsis. Digital examination revealed a normal anus, ampulla, and rectosigmoid. A repeat roentgenogram of the abdomen at this time showed a dilated segment of intestine passing across the epigastrium and vertically in the left upper quadrant (Fig. 2). There was a slight amount of air within the stomach. A presumptive diagnosis of congential intestinal obstruction was made.

The following morning, thirty-eight hours after birth, another flat plate (Fig. 3, *A* and *B*) of the abdomen disclosed marked dilatation of the stomach, entire duodenum, and upper 5 to 6 cm. of the jejunum. Ten cubic centimeters of thin barium were injected into the stomach through a small urethral catheter, and complete obstruction of the jejunum

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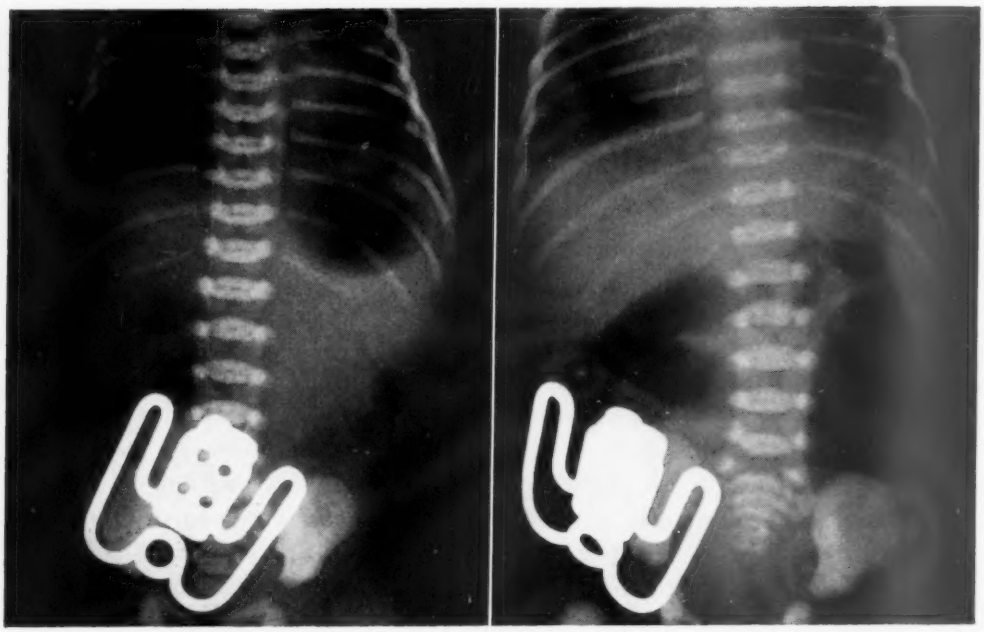
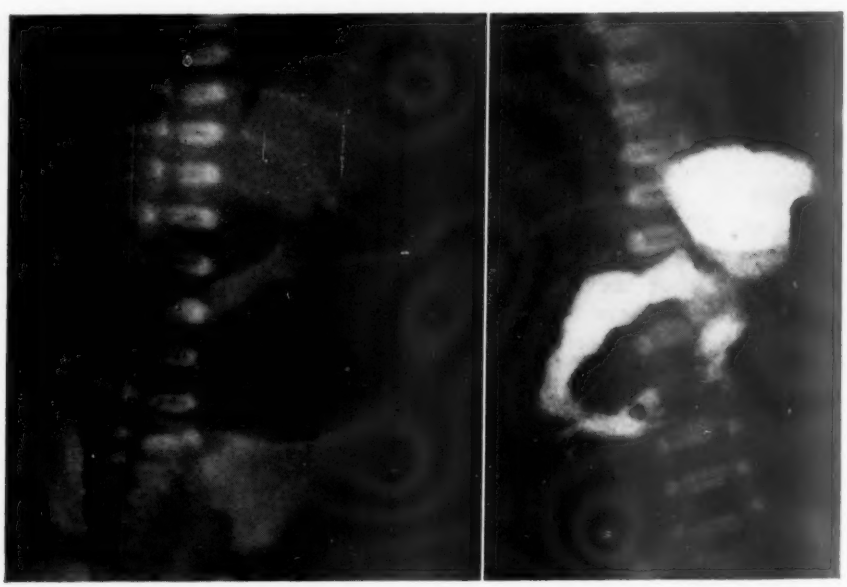


Fig. 1. Fig. 2.

Fig. 1.—Roentgenogram, twenty-four hours after birth, showing air in stomach with no appreciable amount in intestines.

Fig. 2.—Roentgenogram, twenty-nine hours after birth, showing dilated loops of intestines, with exact site of obstruction still obscure.



A. *B.*

Fig. 3.—*A*, Roentgenogram, thirty-eight hours after birth, revealing marked dilatation of the stomach, duodenum, and proximal jejunum with no air in the remaining intestines. *B*, Roentgenogram, thirty-eight hours after birth, with barium outlining the point of obstruction in the jejunum.

was demonstrated 5 to 6 cm. beyond the ligament of Treitz, with associated dilatation above and absence of air below. The barium was partly aspirated and the urethral catheter was left in the stomach for continuous gastric suction.

Roentgenographic studies of the esophagus, lungs, heart, and great vessels appeared normal.

The child passed a small pearly-gray stool thirty-eight hours after birth, and a Farber's test revealed the absence of cornified epithelial cells.

A small polyethylene tube was inserted into the saphenous vein at the ankle, through which fluids, electrolytes, and blood were given in preparation for surgery.

Forty-four hours after birth, an exploratory laparotomy was performed (J. T. A., Jr.) under open-drop ether anesthesia, using a right paramedian rectus-splitting incision. When the peritoneal cavity was entered, a large, dilated loop of intestine presented itself into the incision. No free fluid was noted. Upon exploration, the presenting loop was found to be the proximal jejunum, which measured 4 cm. in its greatest diameter. Approximately 6 cm. below the ligament of Treitz the distention abruptly ceased and beyond this point the jejunum measured only 4 mm. in its greatest diameter (Fig. 4). There was no break in the continuity of the serosa. Upon palpation, a thin membrane was felt occluding the lumen of the jejunum. The remaining gastrointestinal tract showed no anomalies and no meconium was felt within the lumina.

Fig. 4.—Dilated proximal loop of the jejunum with collapsed intestines below point of obstruction.

After placing a rubber-shod clamp across the jejunum just below the ligament of Treitz, the bowel was opened for 2 cm. longitudinally on the antimesenteric border, 2 cm. above the site of obstruction. A congenital diaphragm, completely occluding the lumen, was carefully excised with scissors at its junction with the wall of the jejunum. Small bleeders were controlled with 0000 plain catgut ligatures. The incision in the jejunum was closed longitudinally in two layers, the inner layer with 0000 plain catgut on an atraumatic needle, using an over-and-over stitch, and the outer row with interrupted 0000 silk sutures (Fig. 5). Air and fluid were then expressed from the dilated loop into the collapsed jejunum to demonstrate the patency of the lumen. The abdominal incision was closed in layers, using interrupted silk sutures.

The diaphragm measured 1 mm. in thickness and 20 mm. in its greatest diameter. Microscopically, the diaphragm was composed of normal-appearing jejunal mucosa and submucosa on both sides. No muscle fibers were seen in the septum.

The patient's postoperative course was uncomplicated. Fluids and vitamins were given parenterally, chemotherapy was given intramuscularly, and constant gastric suction was maintained. On the third postoperative day the gastric tube was clamped and the infant was given one ounce of dextrose water every two hours. The following day he passed several small, dark-green stools. On the fifth postoperative day, 4 cm. of lipiodol was injected into the stomach. Two hours later, the lipiodol was seen by fluoroscope to be at a point well beyond the site of the previous diaphragm. The gastric tube was removed at this time. Upon fluoroscopic and roentgenologic examination the following day, lipiodol appeared within the rectal ampulla, establishing patency of the entire gastrointestinal tract.

When sutures were removed on the seventh postoperative day, the incision had healed.

The child progressed well and was discharged when he was 21 days old and weighed four pounds twelve ounces.

He developed normally without any gastrointestinal complaints. Seven months postoperatively, a gastrointestinal series showed that opaque media passed the small bowel without delay and that the site of the previous diaphragm could not be determined by roentgenograms. The child remained in good health when seen at 1 year of age.

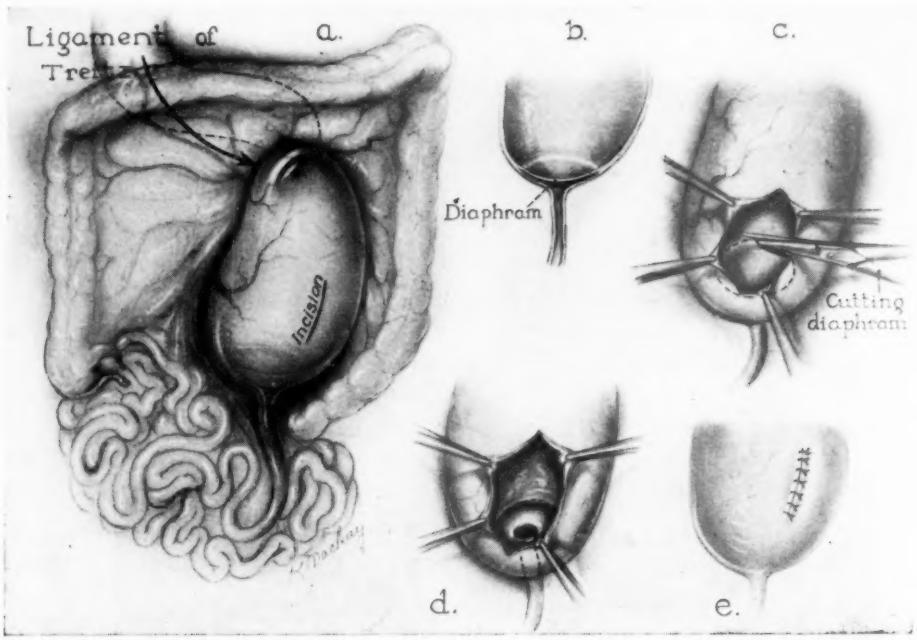


Fig. 5.—Jejunotomy: *a*, site of obstruction; *b*, relation of diaphragm to jejunal wall; *c*, excision of septum; *d*, completed excision; and *e*, closure.

DISCUSSION

The first successful surgical repair of congenital atresia of the intestine by anastomosis of the segments was reported by Fockens,[4] of Rotterdam, in 1910. In the past ten years, the decrease in the mortality rate may be attributed to early diagnosis, prompt surgical intervention, and thorough pre- and postoperative care. Prematurity and the associated anomalies,[5] which occur frequently in these infants, also have a bearing on the survival rate.

Accurate diagnosis of congenital atresia can usually be established within twenty-four to forty-eight hours after birth by a history of emesis, abdominal distention, absence of cornified epithelial cells in the stools, and by flat plate

of the abdomen. In high obstructions, emesis occurs early and there is a striking flatness and emptiness of the lower abdomen. If there is any doubt or confusion as to the interpretation of the flat film, a small amount of thin barium or lipiodol can be injected into the gastrointestinal tract for fluoroscopic examination, and subsequently aspirated. Alternatively, air may be injected, as suggested by Glover.[1]

Decompression of the distended stomach and intestines is instituted by means of an indwelling nasal urethral catheter. Fluids, electrolytes, and blood (totaling 60 to 70 c.c. per pound of body weight every 24 hours) are replaced, pre- and postoperatively, through a small polyethylene tube inserted into the saphenous vein at the ankle.

Open-drop ether anesthesia, without premedication or sedation, has been used successfully in other cases of abdominal surgery of the newborn.[6]

When a definitive surgical procedure is to be performed, such as a Rammstedt pyloroplasty or reduction of an intussusception, the abdomen is opened through a transverse incision. However, when a complete exploration is indicated, because of possible multiple malformations often connected with congenital atresia, a paramedian vertical incision is preferred. With a vertical incision, any point from the duodenum to the peritoneal reflection of sigmoid can be readily reached by the surgeon.

If there is loss of continuity of the intestine, anastomosis is indicated; with multiple areas of atresia, the blind loops can be left undisturbed.

When the obstruction is due to a diaphragm or septum, the site can usually be visualized and palpated as a mucosal partition between the dilated and the collapsed segments of the bowel.

No case of congenital diaphragm of the jejunum treated by jejunotomy and excision, in which the patient survived, has been noted in the literature.

Ladd and Gross,[7] in 1941, stated that it is "preferable to avoid dilating or cutting an obstructing diaphragm, because it is technically quicker and more satisfactory to perform a short-circuiting anastomosis."

Morton,[8] in 1923, after autopsy study, was the first to advocate excision of a congenital diaphragm of the duodenum. He advised ". . . an incision parallel to the long axis of the affected bowel crossing the diaphragm, with complete removal of the membrane and suture of the incision transversally. . . ."

The first case treated by this technique was reported in 1927 by Peterson,[9] who performed a pyloroplasty with removal of a diaphragm from the duodenum. The patient died a few hours later. In 1932, Morton and Jones[10] successfully performed a duodenotomy with complete removal of the diaphragm by fulguration. Glover and Barry,[1] in 1949, reported the successful excision of duodenal diaphragms in two patients. A third patient died eight hours after excision of a diaphragm of the ileum.

In this instance it seemed technically easier, safer, and more physiologic to perform an enterotomy with complete excision of the diaphragm rather than a short-circuiting anastomosis.

The diaphragm (Figs. 4 and 5) was not located at the narrowest point of the bowel; it had stretched under pressure and the intestine was dilated for a short distance below it.

The longitudinal antimesenteric incision proximal to the diaphragm permitted excision by sharp dissection under direct vision. The enterotomy could then have been closed either longitudinally or transversally, depending on the amount of dilatation.

Patency was insured by expressing fluid and air through the site of the excised diaphragm; the nasal urethral catheter was left in the stomach for continuous decompression until normal physiology of the intestine was established, after which fluid was permitted by mouth. Prior to removal of the tube, 5 c.c. of lipiodol was injected into the stomach and a fluoroscopic examination was made to demonstrate patency of the entire intestinal tract.

SUMMARY

A case of congenital atresia of the jejunum due to a mucosal diaphragm was successfully treated by enterotomy and excision of the obstructing septum. The authors have given their reasons for preferring this procedure to traditional short-circuiting anastomosis.

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PARTIAL HEPATECTOMY FOR METASTATIC CARCINOMA OF THE LIVER

Report of a Case With Unusual Features

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PRIOR to a decade ago metastatic carcinoma of the liver, regardless of the extent or primary source, was regarded as an unquestionable criterion of inoperability for cancer, either for cure or for palliation. In the last decade this concept has been challenged by several surgeons. Cattell,[1] in 1940, reported the sucessful resection of a large, apparently solitary metastasis in the right lobe of the liver in a 70-year-old patient with carcinoma of the rectum. The metastasis was excised at the first stage of a two-stage Lahey resection of the primary growth. The pathologic report was adenocarcinoma with no involvement of the mesenteric lymph nodes but with blood vessel invasion. This suggested that the hepatic metastasis was actually an embolic spread through the superior hemorrhoidal vein, a pathway on which Coller reported. This patient died of intercurrent causes after surviving almost three years.

Since then, several other authors have elaborated on this subject. Wangensteen,[2] in 1945, propounded the thesis that if at the first operation the local lesion and the lymphatic drainage area can be satisfactorily excised, secondary excision of the hepatic metastasis six to eight weeks later may cure the lesion Brunschwig[3-5] has emphasized several notable points (to be discussed later) and has stated that not enough cases have been reported as yet to draw statistically valid conclusions.

It seems worth while, therefore, to add to the literature the preliminary report of a case which fulfills Wangensteen's dictum and presents a few unusual features.

CASE REPORT

On Nov. 20, 1951, an anterior resection of the sigmoid for carcinoma was performed on a 73-year-old white woman E. B. (No. 709160) through a lower left rectus abdominal incision. Upon exploration of the abdomen there was no gross node involvement and no other local evidence of carcinoma noted. On the anterior surface of the liver in the quadrate lobe there could be felt a well-circumscribed 3 by 3 cm. firm mass. The remainder of the liver surface was smooth. With retraction of the anterior abdominal wall, the liver nodule could be visualized as whitish gray, but was not accessible to excision with safety. A needle-aspiration biopsy was performed and reported as showing cells consistent with metastatic carcinoma. The sigmoid resection was performed with a wide margin of bowel and mesentery and a two-layer end-to-end anastamosis. On the fourth postoperative day a decompression cecostomy was performed because of moderate distention. The patient had an uneventful convalescence. The pathologic report was adenocarcinoma of the sigmoid, grade two, with

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all nodes examined negative, and with an adequate margin of normal bowel and mesentery resected.

One month following the resection of the primary lesion the patient was readmitted. The abdomen was re-explored through an upper right rectus incision. The entire surface of the liver was carefully inspected and palpated. The only suggestion of metastatic disease was the nodule noted at the original operation. This was confined to the quadrate lobe directly overlying the hilar structures. A double row of deep mattress sutures of No. 1 chromic catgut was placed circumferentially for hemostasis and the entire lobe was resected. There was minimal bleeding and bile drainage. Since the resection was too extensive to permit approximation of the liver edges, the cavity was lined with Gelfoam and the ends of the mattress sutures tied over it. The common duct, hepatic artery, and portal vein were clearly exposed. The abdomen was closed, the resected area being drained through a lateral stab wound in anticipation of bile drainage. There was minimal drainage from the abdomen; the postoperative course was uneventful. The patient was discharged on the eleventh day and has remained well. The pathologic specimen showed a solitary large metastatic nodule confined to the quadrate lobe of liver and surrounded by adequate surgical margins.

DISCUSSION

Churchill[6] and others, demonstrating long survival period (over thirteen years) and presumed clinical cures following resection of solitary lung metastases, have established by work done prior to a decade ago the rationale of surgical extirpation of metastatic cancer of the lung. Despite this fact the clinical demonstration of apparent metastatic cancer of the liver during abdominal surgery, until recently, has almost universally been regarded as a hopeless prognostic sign in all cases, not infrequently lacking histologic proof of metastasis.

Brunschwig has pointed out that frequently it is impossible to determine by inspection or palpation whether a solitary liver nodule is benign or malignant and that the presence of a subcapsular nodule in the liver when there is a resectable cancer elsewhere in the abdomen should not deter removal of the latter because the nodule is assumed to be metastatic. He emphasizes that frequently when such nodules are excised and histologically examined they are found to be fibromas, scirrhous angiomas, or cysts. Biopsy and frozen section should be carried out before final decision in regard to the nature of the procedure for the primary cancer. Since instances of solitary hepatic metastases are not extremely rare at necropsy, excision of all macroscopic neoplastic tissue, particularly solitary nodules, should be performed. This affords the full benefit of surgical therapy and there is no other treatment available.

In the case here reported, the primary lesion was resectable with adequate surgical and mesenteric margins and there were no lymph nodes involved. While one cannot state with certainty that deeper metastases might not be present, a careful inspection under direct visualization and palpation failed to demonstrate any. The metastatic nodule lay in the quadrate lobe overlying the vital structures and was completely excised with adequate surgical margins. The patient had a short, uneventful postoperative course. While no claim is made for cure at this time, the dangerous location of the metastatic lesion, if unexcised, would soon have involved the vital structures. It seems, therefore, reasonable to suggest that longer life, good palliation, and a reasonable chance of cure have been afforded.

SUMMARY AND CONCLUSIONS

1. Until recent years the presence of metastatic cancer of the liver has denied the patient, in many instances, reasonable treatment and has implied a universally hopeless prognosis.

2. Several surgeons have challenged this concept both on theoretical and practical grounds. With resection of the metastatic disease in selected cases a few early cures have been reported.

3. Partial hepatectomy, formerly a procedure of prohibitive magnitude, can now, with the advent of modern anesthesia, surgical techniques, and blood banks, be undertaken with safety.

4. It seems reasonable to assess each case individually depending on the abdominal findings at operation, and to undertake that procedure best suited for each case. It is mandatory to prove histologically the presence of metastatic disease before denying the patient the only chance of cure.

5. Solitary liver metastases, surgically accessible, have been demonstrated at necropsy and are not rare.

6. Cures are possible in some cases, palliation certain in a larger number.

7. The number of cases thus far reported is too small to draw statistically valid conclusions.

8. This is a preliminary report of a case successfully treated with surgical excision of a primary carcinoma of the sigmoid and of the entire quadrate lobe of the liver for an apparently solitary metastasis overlying the vital structures. Palliation has been afforded and it is suggested that a cure is possible.

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SIMULTANEOUS OCCURRENCE OF VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS AND OSTEITIS FIBROSA CYSTICA

Report of a Case Showing Both Diseases in Addition to Liposarcoma

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TWO diseases described by Friederich Daniel von Recklinghausen, the late German pathologist, still carry his name. Although there are similarities between neurofibromatosis (von Recklinghausen's disease) and generalized osteitis fibrosa cystica (von Recklinghausen's disease) they are separate and distinct disease entities. It has been suggested[3, 14] that occasionally the two conditions are associated, and Thannhauser[16] has discussed the possibility of a common pathogenesis. In reviewing the literature we can find no case in which both diseases were proved to be present.

Von Recklinghausen's neurofibromatosis was described in 1882 as a disease of the peripheral nerves. Since that time many additional clinical manifestations of this bizarre and protean disease have been discovered. Strong hereditary and familial features have been found to be present in generalized neurofibromatosis.[15, 17] The lesions may involve any part of the nervous system with resultant subcutaneous nodules, skin pigmentation (café au lait spots), mental deficiency, and changes in the bones, joints, vessels, and lymphatics.[12] The tumors are thought to arise as proliferations of the sheath of Schwann but this origin is not uniformly accepted. Aegeter[1] suggests that the disease consists of "true neoplasms (neurilemmoma, melanoma, and glioma) and hamartomatous proliferations." These patients frequently have lipomata also.

In contrast, generalized osteitis fibrosa cystica (von Recklinghausen, 1891) has been proved to be caused by hyperparathyroidism resultant from hyperplasia, adenoma, or carcinoma of the parathyroid glands. There is no familial or hereditary tendency in this disease. It is manifested by skeletal and/or urinary tract changes and characteristic laboratory findings. In occasional cases there is no urinary tract or bone disease. Symptoms vary and are divided into three groups dependent on the amount of involvement of each of these systems.[2] There may also be symptoms due to decreased hematopoietic function. After surgical removal of the adenoma or hyperplastic parathyroid tissue, the blood chemistry returns to normal and there is cessation of the progression of skeletal and urinary tract lesions. After a period of months or years the bones are recalcified and assume a more normal appearance.

Skeletal changes occur in both diseases of von Recklinghausen. According to Fairbank[5] scoliosis is present in about one-half of the cases of neurofibromatosis while bone changes are found in 7 per cent. Abnormalities of growth occur

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with resultant increased length or over-all hypertrophy of the involved bones while others may have shortening or congenital absence of certain bones.[12] Pseudoarthrosis may also occur as described by Ducroquet[4] and others[8, 13] while spondylolisthesis and melorheostosis are sometimes found.[12] Subperiosteal "bone cysts" are due to pressure of the neoplasm causing an indentation in the bony cortex.[17] A shell of bone may be laid down by the periosteum completely enclosing the tumor.

The roentgenologic appearance varies with the type of bony involvement. There may be smooth erosion of the cortex by a periosteal neurofibroma or a cortical cyst. The adjacent bone frequently shows increased density. There may be increased density of the shaft of a long bone without obvious erosion of the cortex. Some of the "cystic" lesions in long bones appear to be endosteal in origin. An intraosseous neurofibroma at the site of a tibial fracture was reported by Green and Rudo[8] and similar tissue was found filling the marrow of the lower end of the femur in one of Friedman's[7] cases. The exact pathogenesis of the endosteal lesions is not known, but MacKenzie[11] suggests that they probably arise from "nerve endings which penetrate into the bone with the nutrient vessels." The structure of new bone which is laid down is abnormal, appearing amorphous and not trabeculated.[11] The skull rarely shows changes consisting of increased or decreased thickness.

Skeletal changes in hyperparathyroidism are due to increased urinary excretions of calcium and phosphorus with resultant decalcification of bone. These changes may be absent even in severe cases while others show widespread demineralization of the entire skeleton and many types of skeletal deformities.[10] When it does occur, the bone disease consists of generalized decalcification with superimposed cysts and tumors.[2] In some cases there are true cysts lined with fibrous tissue and filled with fluid. The bone tumors consist of solid masses of soft tissue and may give the appearance of cysts. These cysts may give rise to symptoms either by tumor formation or by causing pathologic fractures. Cysts occur most frequently in the jaws, metacarpals, metatarsals, or in the ends of long bones.[2] The amount of decalcification varies and results in numerous types of deformities including "pigeon breast" deformity of the chest, decrease in stature, bending of long bones, pelvic deformities, and others.[2] Roentgenologic diagnosis of this disease is made by evidence of generalized decalcification. There is a fibrous appearance of the long bones, an even ground-glass appearance of the skull in addition to the "cystic" areas. The latter tend to be small and numerous and may be difficult to see because of the lack of calcium in the surrounding bone.[9] Strock[15] has emphasized the characteristic changes in dental roentgenograms. In contrast to the jaws, the teeth do not show decalcification but the lamina dura is frequently not visible.

We have recently treated a patient who was admitted because of a large liposarcoma. He was also found to have both types of von Recklinghausen's disease.

CASE REPORT

W. J. D., a 42-year-old white man, was admitted Jan. 7, 1952, complaining of a mass on his left shoulder. He stated that this had been present for about fifteen years. Six weeks

prior to admission the tumor had become "infected" and ulcerated. The ulcer did not heal so he sought medical assistance. He also said that he had many smaller nodules over the body which were asymptomatic and were of shorter duration.

Past history revealed that he had a fractured pelvis treated elsewhere in 1946. He denied other serious injuries, illnesses, and operations.

Review of systems was essentially negative. He had had slight pedal edema and occasional dyspnea on exertion but no chest pain or hemoptysis. Syncopal attacks had occurred in the past but not recently. His appetite was good and he denied weight loss. There was no history of nausea, vomiting, constipation, or melena. He had had hematuria one or two times but denied passage of urinary calculi, frequency, and nocturia.

There was no family history of skin nodules. One sister had diabetes but there were no other hereditary or familial illnesses.

Fig. 1.

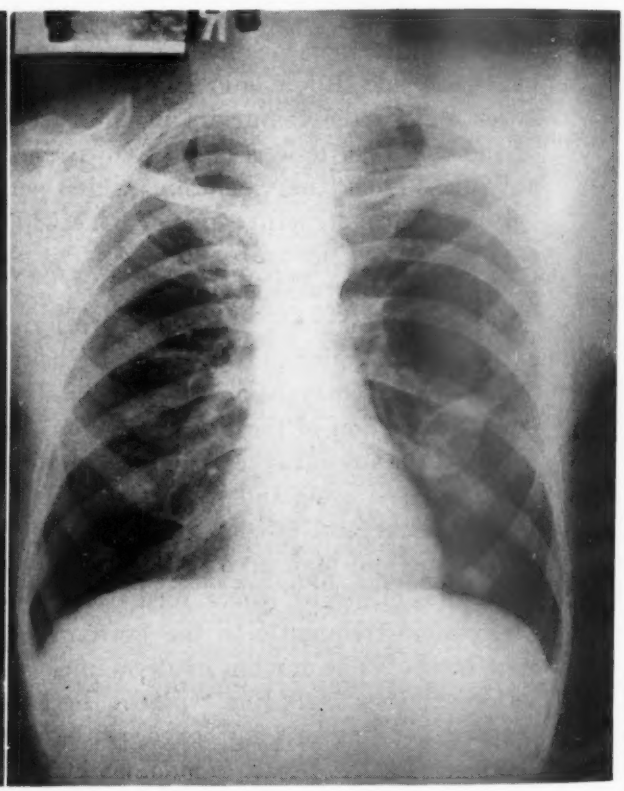

Fig. 2.

Fig. 1.—View of large tumor on posterior aspect of shoulder, multiple smaller subcutaneous nodules, and café au lait spots.

Fig. 2.—Roentgenogram showing cystic expansion of anterior end of left fourth rib.

Physical examination revealed a poorly nourished white man who did not appear acutely ill. There were multiple subcutaneous nodules over the body, typical café au lait spots, and a large, ulcerated tumor mass overlying the left scapula (Fig. 1). The head appeared normal except for the subcutaneous nodules. Examination of the eyes, ears, nose, and throat revealed no abnormalities. There were several subcutaneous nodules in the neck but the thyroid was not palpable and there were no enlarged lymph nodes. There were moist râles and bronchial breath sounds over both lung bases. There was a fusiform swelling at the anterior end of the left fourth rib. The heart rate was 68 and the rhythm regular. There was no evidence of cardiac enlargement and no murmurs were heard. Blood pressure was 118/80. The

abdomen was flat and there were no scars. The liver was palpable just below the right costal margin but there were no other palpable intra-abdominal organs or masses. The extremities were symmetrical and peripheral arterial pulsations were normal. Reflexes were physiologic. The genitalia were those of a normal adult man.

Laboratory findings were as follows: Hemoglobin 10.5 Gm., R.B.C. 3,060,000, W.B.C. 7,000 with a normal differential. Urinalysis was negative.

Roentgenograms revealed a definite expansion of the anterior end of the left fourth rib with numerous radiolucent areas (Fig. 2). The left shoulder showed irregular areas of radiolucency in the neck and head of the humerus. These findings were considered as consistent with medullary-type neurofibromatosis involving bone.

A biopsy was taken from the ulcerated tumor which showed structure that was consistent with liposarcoma.

Fig. 3.—Cross section of liposarcoma after removal.

On Jan. 17, 1952, the large tumor and part of the underlying trapezius muscle were excised. The defect was covered with a split thickness skin graft. One of the subcutaneous nodules was excised and a biopsy was obtained from the left fourth rib. The patient had an uneventful postoperative course.

Pathologic Findings.—Grossly the tumor was hemispherical, weighed 800 Gm., measured 6 by 15 by 15 cm., and was overlain by a circular excision of skin that measured 12 cm. in diameter. Slightly off center a soft, mushroomlike growth, measuring 3 by 6 cm., appeared to herniate through a smaller defect in the skin. On section this was found to merge with a subcutaneous ovoid component, measuring 7 cm. in its greatest dimension, which could be

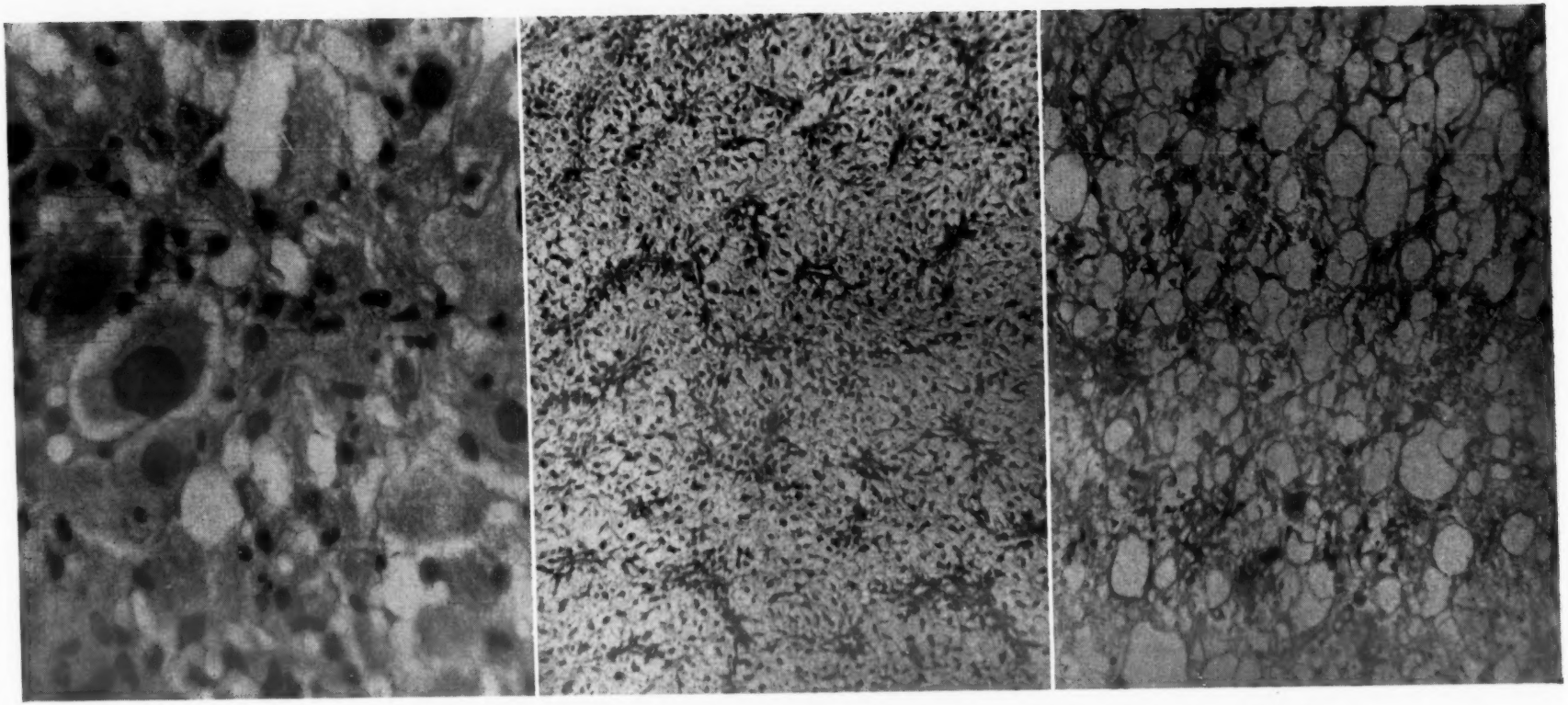

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Section from fungating portion of liposarcoma.
Fig. 5.—Section through centrally located component of liposarcoma.
Fig. 6.—Section through periphery of liposarcoma.

partially shelled out of its central concave bed in the larger tumor mass (Fig. 3). The cut surfaces of the fungating portion were indistinctly lobulated and grayish yellow with hemorrhagic streaks. The central subcutaneous mass to which this lesion was connected showed lobulated, transparent, myxoidlike surfaces on section. The total growth had a delicate fibrous capsule over its base and margins and was underlain by the deep fascia to which strips of striate muscle were attached. The surfaces of the remaining deeper portion showed lobulation, lemon yellow color, and a scattering of barely palpable, white nodules (1 to 3 mm.) which occurred along the course of delicate transparent strands traversing the lobules.

There were two additional specimens—a sliver of cortical-type bone that measured 0.5 by 0.7 by 2 cm., and an elliptical excision of skin and subcutis that contained a non-encapsulated, fibrous-appearing thickening in the corium that measured about 1 cm. in diameter.

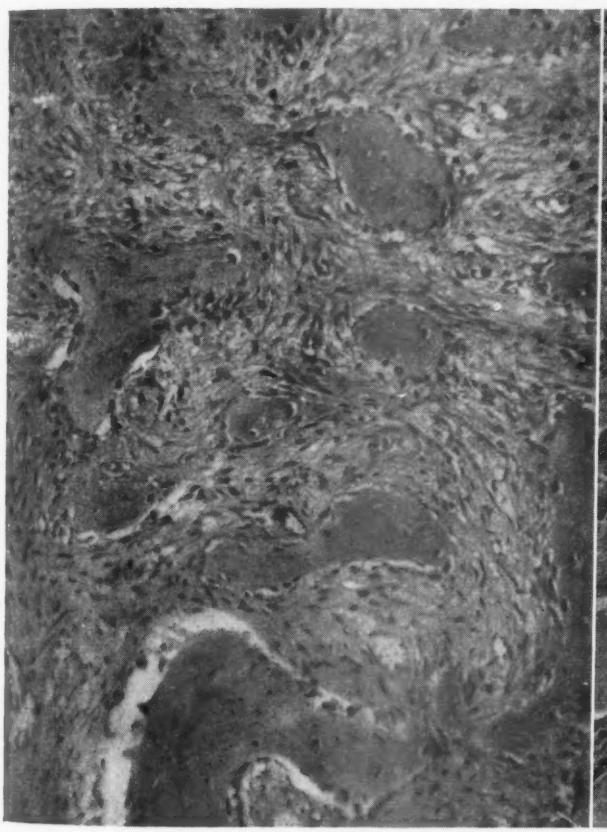

Fig. 7.

Fig. 8.

Fig. 7.—Biopsy of rib showing structure of osteitis fibrosa cystica.
Fig. 8.—Cyst lining showing giant cells.

Microscopic Examination.—In the fat tumor the structure was quite varied. Sections from the fungating part showed the picture of cellular, fully developed liposarcoma (Fig. 4). Here all traces of adult fat structure had been obliterated by spindle, ovoid, and giant cells, with vesicular hyperchromatic or pyknotic nuclei, numerous mitoses, vacuolated cytoplasm, and scant intercellular fibrils. In sections from the subcutaneous centrally located component the structure was predominantly myxomatous in character (Fig. 5). Numerous capillaries formed a plexiform pattern with the interstices containing loosely arranged small

spindle and stellate cells, which usually gave rise to short processes. In the remaining part of the tumor adult fat cells were present but always in association with abnormal changes in the interstitial and septal element. This latter was so diffuse as to make it difficult to find an area as large as a low-power microscopic field that was free from it. In some areas the fat spaces had been crowded out largely by edematous connective tissue with only a scattering of nuclei of uniform size and staining quality. However, for the most part the

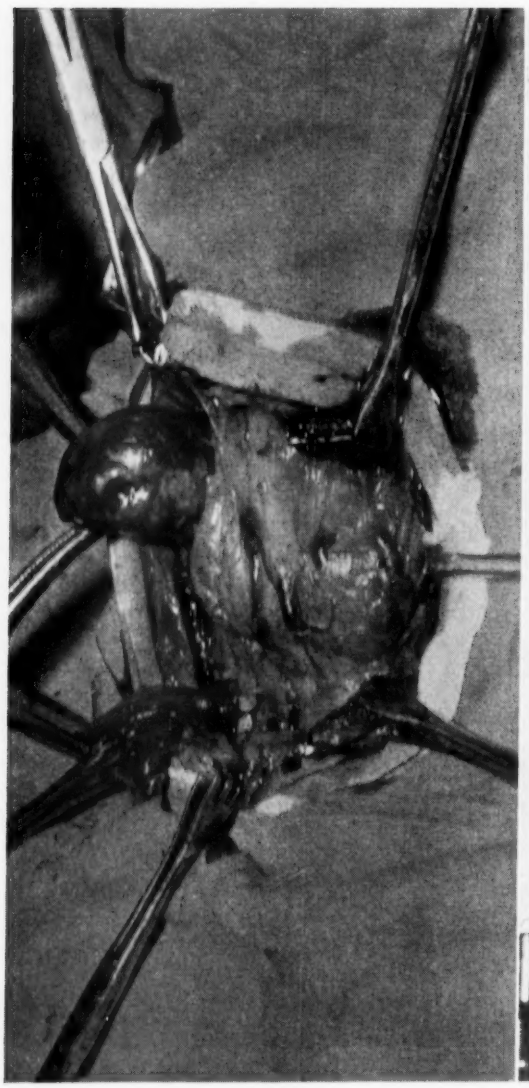

Fig. 9.

Fig. 10.

Fig. 9.—Parathyroid adenoma arising at right inferior pole of thyroid gland. The tumor has been displaced upward from its bed.

Fig. 10.—Cross section of parathyroid adenoma.

collagenous element was less prominent and tended to have "knotty" distribution. Spindle, ovoid, and bizarre giant cells with overnourished nuclei were present in varying numbers throughout such areas (Fig. 6).

The biopsy of the lesion of the rib showed the structure of osteitis fibrosa. In the sections one observed vascular connective tissue surrounding and separating spicules of new

bone and osteoid tissue as well as areas showing numerous multinucleated giant cells and a dusting of hemosiderin in background of connective tissue (Figs. 7 and 8).

The small skin tumor was characteristic of neurofibroma. The sections revealed an unencapsulated growth of wavy fibrils and bands of fibrous-appearing tissue distributed in a haphazard fashion.

On Feb. 2, 1952, blood chemical studies showed serum calcium 15.4 mg. per cent, phosphorus 2.9 mg. per cent and alkaline phosphatase 3.09 Bodansky units. Blood urea nitrogen was 28.3 mg. per cent and serum protein 6.3 Gm. with an A/G ratio of 1.69/1.00. Urine calcium excretion was 232 mg. during twenty-four hours after having been placed on a low calcium diet. Repeat serum calcium was 14.5 mg. per cent, phosphorus 2.25 mg. per cent and alkaline phosphatase 4.7 Bodansky units. Twenty-four hour urine calcium excretion was 259 mg.

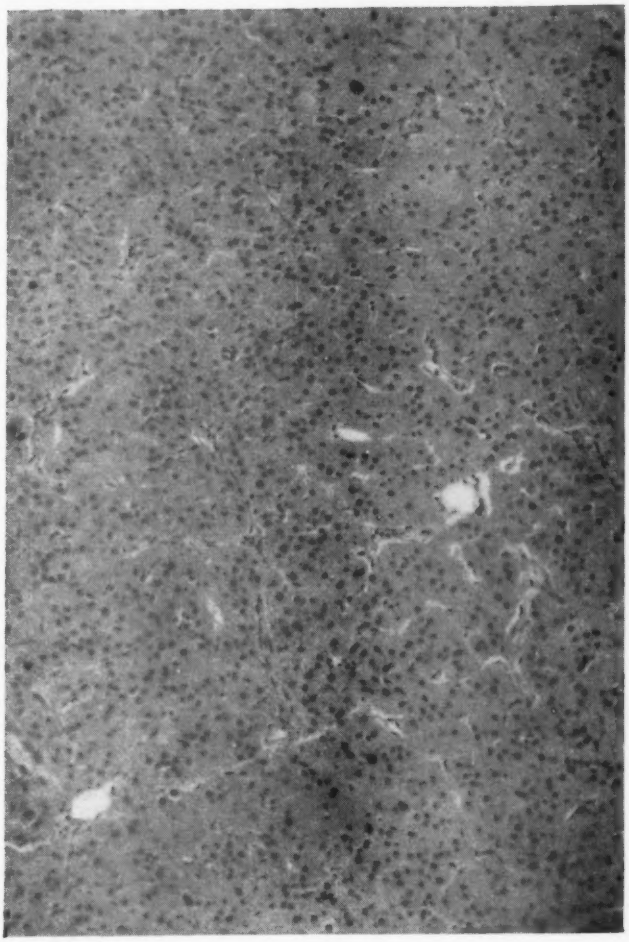

Fig. 11.—Microscopic section of oxyphil adenoma of parathyroid.

Roentgenograms of the spine and pelvis were obtained which showed irregular radiolucent areas involving the left ileum and cystic areas in the intertrochanteric region of the right femur. There was evidence of a healed fracture of the right pubic arch and demineralization of the bones in general. There was no evidence of urinary calculi.

On Feb. 27, 1952, the neck was explored and a parathyroid adenoma measuring 4.2 by 3 by 2 cm. was found at the right inferior pole of the thyroid and extending posteriomedially between the trachea and esophagus (Fig. 9). This was removed without difficulty. The other parathyroids appeared normal.

Pathologic Findings.—Grossly the parathyroid tumor was elliptical, weighed 20 Gm. and measured 2.5 by 3 by 4.2 cm. It was soft but not fluctuant, and showed an intact capsule through which coursed prominent branching veins. Section disclosed fragmentation with the formation of linear breaks in the tissue that contained blood. This was thought to be due to trauma of removal rather than spontaneous cystic change. At one extremity where the tissue appeared intact the surfaces were light brownish red and lobulated (Fig. 10). Microscopically it showed the structure of oxyphil adenoma. The sections revealed fairly closely packed polyhedral and cubical eosinophilic cells in trabecular arrangement. There was some variation in the size and staining quality of the nuclei but no mitotic figures or capsular invasion could be demonstrated (Fig. 11).

Postoperatively the blood chemistry changed rapidly. On the first postoperative day serum calcium was 14.1 mg. per cent, phosphorus 1.1 mg. per cent, and alkaline phosphatase 4.0 Bodansky units. Twenty-four hours later the serum calcium was 11.2 mg. per cent, phosphorus 3.3 mg. per cent and alkaline phosphatase 4.3 Bodansky units. On the fifth

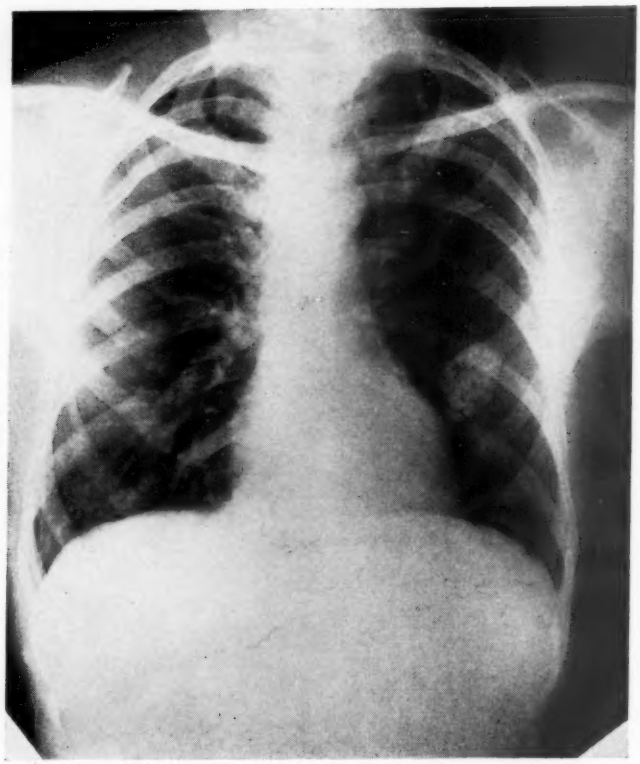

Fig. 12.—Chest roentgenogram three months after removal of parathyroid adenoma showing recalcification in cystic area of fourth rib.

day serum calcium was 10 mg. per cent, phosphorus 3.2 mg. per cent, and alkaline phosphatase 4.9 Bodansky units. These levels were maintained essentially unchanged until the patient was discharged ten days later. He was given large amounts of calcium gluconate and irradiated ergosterol postoperatively and showed no signs of tetany. He was discharged symptom free on calcium gluconate on March 14, 1952.

He has been seen several times since his discharge and has remained asymptomatic. He has gained approximately twenty pounds since surgery. Skeletal survey on June 16, 1952, showed considerable recalcification in the areas of cysticlike bone destruction (Fig. 12).

COMMENT

In retrospect, the bone changes in this case are more typical of osteitis fibrosa cystica than neurofibromatosis. Biopsy and blood chemistry confirmed the diagnosis and the parathyroid adenoma was removed.

Cases of neurofibromatosis with bone changes should be studied carefully because of the rare simultaneous occurrence of hyperparathyroidism.

SUMMARY

A case with liposarcoma, neurofibromatosis (von Recklinghausen), and osteitis fibrosa cystica (von Recklinghausen) is presented. The similarities and methods of distinguishing the two diseases of von Recklinghausen are discussed.

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Editorial

Chronic Cholecystitis With Superimposed Acute Cholecystitis

THE nature of chronic cholecystitis, its etiology, and its evolution are poorly understood. Chronic cholecystitis is often assumed to be the sequel of an acute inflammatory process in its subsiding or healing state. Actually other factors may produce the chronic inflammatory reaction such as intermittent or continuous abnormal composition of the bile, attenuated or ordinarily nonpathogenic enteric organisms, and the presence of pure gallstones or mulberry-shaped mixed gallstones. No two gall bladders with chronic cholecystitis are exactly alike. They have, however, one feature in common, namely that they contain gallstones. In some, the gallstones caused the chronic cholecystitis. In others, the gallstones are the result of the chronic cholecystitis. Familiarity with the chemical composition and structure of gallstones aids in ascertaining whether they are the cause or the effect of the chronic cholecystitis.

Chemical analyses reveal that three normal constituents of the bile—cholesterol, calcium bilirubinate, and calcium carbonate—are the principal stone-forming substances. About 10 per cent of gallstones—the pure gallstones—are composed almost entirely of one of these substances. About 80 per cent—the mixed gallstones—are a mixture of these components in varying proportions. The remaining 10 per cent—the combined gallstones—are a combination in which one kind of gallstone forms the nucleus and another the shell. Pure gallstones form when the bile contains intermittently or continuously an excess of one of the stone-forming substances. This excess is due to a disturbance of metabolism or of liver function rather than to an inflammatory reaction of the gall bladder or biliary ducts. Mixed gallstones, on the other hand, form when the function of the gall bladder is so altered that the solvents, bile acids, are resorbed faster than the stone-forming constituents that they hold in solution. This creates opportunities in the gall bladder for further concentration, precipitation, and crystallization of these substances. Combined gallstones include the ingredients of pure and of mixed gallstones, with the one kind of stone forming the nucleus and the other the shell. They form when the two conditions for the formation of gallstones occur in either sequence. Thus mixed or combined gallstones are the sequel to chronic cholecystitis, while pure gallstones may be the cause.

Acute cholecystitis occurs over ten times more frequently in gall bladders that contain gallstones than in normal gall bladders. All gall bladders removed surgically for acute cholecystitis that contain gallstones are in fact gall bladders with the acute cholecystitis superimposed on a chronic cholecystitis. Grossly such a gall bladder differs little from one with acute cholecystitis except for the presence of calculi within the viscus. Microscopically, however, the effects of

the chronic inflammatory process are in evidence. These are hypertrophy of the muscular coat, outpouchings of the mucosa toward the external layers, the so-called Rokitansky-Aschoff sinuses, an increase of the connective tissue, particularly in the perimuscular layer, and varying degrees of infiltrations with lymphocytes, plasma cells, large mononuclear cells, and some eosinophilic granulocytes. Superimposed on the chronic process is an acute inflammatory reaction. A hemorrhagic fibrinopurulent exudate covers the denuded or ulcerated areas of the mucosa. All the layers are markedly spread apart by inflammatory edema and are infiltrated with freshly extravasated erythrocytes and neutrophilic granulocytes. The serosal surface is covered by fibrin.

Experience has shown that cholelithiasis is a predisposing factor to acute cholecystitis. Just as a patient with an inguinal hernia lives in the shadow of incarceration of the hernial content, also a patient with cholelithiasis may at any time develop acute cholecystitis superimposed on the already existing chronic cholecystitis. In fact a patient having chronic cholecystitis with cholelithiasis is ten times more likely to develop acute cholecystitis than an individual having a normal gall bladder. Therefore the presence of gallstones in the gall bladder is an absolute indication for cholecystectomy.

—*Béla Halpert*

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

POLYPS AND ADENOMAS OF THE STOMACH

LYLE J. HAY, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery of the University of Minnesota Medical School)

THE significance of adenomas and other polyps of the stomach is derived from two sources: First, the manifestations of the tumors per se leading to symptoms from bleeding, ulceration, and changes in the motor function of the stomach. These jeopardize the carrier's health. Second, the possibility of malignant degeneration in these tumors which threaten the patient's life.

The thesis is broadly accepted that the earlier a malignancy is discovered and removed or destroyed the better is the prognosis. The elimination of precancerous lesions such as dermal keratoses, skin burned by roentgen radiation, benign moles, gastrointestinal polyps, and thyroid adenomas, is generally accepted. The poor prognosis in most malignancies attacked by the most thorough methods certainly indicates that the only real promise of a great reduction in morbidity and mortality in the near future lies in earlier diagnosis and treatment of malignancy and especially in elimination of the precursor lesion.

The establishment of adequate data on the incidence of precursor lesions of carcinoma and the relationship of these lesions to malignancy should be one of the more productive methods of lowering the death rate from this affliction. These data are more essential in precancerous lesions of the stomach than in most of the other lesions mentioned, because a laparotomy including gastrotomy, partial gastrectomy or even a total gastrectomy will be required. Such procedures entail a real and appreciable mortality and morbidity. These must be weighed against the dangers of malignant degeneration, obstruction, bleeding, and so forth. This study was suggested by the removal of most of the stomach from patients who were completely or nearly asymptomatic. Examination of the specimens showing one or many small and benign-appearing lesions, and caring for the patients during convalescence, suggested that perhaps the risk accepted by patients treated surgically was greater than those untreated. This study was undertaken in an attempt to clarify the points of the differential diagnosis of malignant adenomas, benign adenomas, and benign gastric tumors other than adenomas and to document the history of benign lesions clinically diagnosed as adenomas which had been observed for long periods.

This presentation is based upon work done under The United States Public Health Service Grant C-298(C5).

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DEFINITION OF TERMS

The term polyp will be used to describe gastric mucosal tumefactions or protrusions which are visible to the gastroscopist or which cast negative shadows during barium-contrast roentgenograms of the stomach. Although we recognize that "polyp" indicates a pedunculated growth from a mucous surface we will use the term to indicate all the histologically unidentified lesions which were encountered. When the pathologic examination has established the identify of the lesions the term "adenoma" will be used. The primary effort has been to determine the characteristics of adenomas. In the nonoperated groups such lesions as fibromas, leiomyomas, hypertrophic gastritis, and pseudopolyps may be included. However, our experience indicates that when a real effort is made by the gastroscopist and roentgenologist and the clinician recognizes the infrequency of occurrence of normal gastric acidity in association with gastric adenomas, most nonepithelial tumors will be eliminated. In the lesions identified by pathologic examination only epithelial tumors, i.e., adenomas, are included. The terms polyposis and adenomatosis are used to designate three or more tumors after the practice of Brunn and Pearl.[3]

HISTORY

Gastric polyps have been known for three centuries. First carefully described by Morgagni in 1761 as an autopsy finding, the first clinical diagnosis was recorded by Quain in 1857.[21] Menetrier described gastric adenomas in 1888. His descriptions of the formation of adenomas by hypertrophy and proliferation of the cells and gastric glands with the resultant formation of cystic and solid adenomas were clear. He believed that these lesions nearly always occurred in a mucosa affected by chronic gastritis, that the usual adenoma remained benign but that malignant change sometimes occurred.[10]

The development of the roentgen ray for diagnostic purposes opened a new avenue for the diagnosis of lesions of internal organs. Spriggs and Marxer credit Heinz (1911) with the first roentgenologic demonstration of a gastric polyp using contrast media.[21]

Roentgenologic diagnosis of polyps of the stomach was well developed when Schindler (1922) diagnosed his first gastric polyp with the gastroscope.[3] The importance of roentgen diagnosis is evidenced by the fact that fifteen of the eighty-four cases of diffuse gastric polyposis reported by Brunn and Pearl (1926) were diagnosed by roentgenography. There was an ante-mortem diagnosis in only seven additional cases, all by operation.[3]

Most cases reported in the literature have had lesions showing malignant degeneration or producing symptoms of a severity demanding therapy. More widespread use of roentgenology and gastroscopy, as well as improved techniques,[15, 21] has resulted in the diagnosis of gastric polyps while they were nearly or completely asymptomatic.[4] The recommendation of therapy at this stage is necessarily based on future potential danger. The majority of authors have regarded the diagnosis of a gastric polyp as an indication for its removal. More recently the recommendation of observing certain lesions has been forthcoming.[4, 13, 21]

Material (see Table I).—

The patients included in this study were selected from a group with small gastric tumors seen prior to 1948. The majority of lesions seen clinically are epithelial in origin, i.e., adenomas and papillomas. Since occasionally foreign bodies and more commonly polypoid hyperplasias of the mucosa may be diagnosed as polyps, we accepted only those clinical cases which were seen on two occasions by either roentgenography, gastroscopy, or by both methods.

TABLE I. PATIENT MATERIAL

GROUP DESIGNATION	NUMBER OF CASES	DESCRIPTION
1	11	Patients with three or more polyps diagnosed clinically as adenomas and not operated upon
2	26	Patients with single or double polyps diagnosed clinically as adenomas and not operated upon
3	11	Patients with carcinoma of the stomach associated with three or more benign adenomas (all treated by gastric resection)
4	10	Patients with three or more benign adenomas treated by gastric resection or polypectomy
5	15	Patients with single or double adenomas treated by gastric resection
6	7	Patients with single or double adenomas treated by gastrotomy and polypectomy
7	17	Patients with cancer associated with single or double adenomas, apparently originating from an adenoma or of a size and conformation making differentiation difficult

Where histologic determination of the type of growth was made, only adenomas were included. The patients with cancer included in the group were those with polypoid lesions whose differential diagnosis was a problem, and those whose stomachs contained a cancer and benign adenomas.

The patients with carcinomas were divided into two groups. In the adenomatosis group there was necessarily always an association of benign adenomas with malignancy. The group with single or double adenomas included two types of patients. The first were those in whose stomachs one or two adenomas were associated with a carcinoma. The second type of patient was that with a carcinoma apparently originating from an adenoma or of a size and conformation which did not permit easy or precise differentiation from a polyp.

INCIDENCE

The incidence of gastric polyps in patients seen clinically is unknown and will remain so because many of these lesions are asymptomatic. Spriggs and Marxer found thirty cases in 4,424 roentgen examinations of the stomach. The importance of any selection is indicated by the findings at the University of Minnesota Cancer Detection Center. Doctors there found thirty-five polyps in 1,330 achlorhydric patients, five in 115 patients with pernicious anemia and three in 271 patients with hypochlorhydria. Only one polyp was detected in the remaining 300 patients examined because of anemia, positive stool examination for blood, or because a relative had gastric cancer.[22] Similar studies conducted on patients selected by being in the cancer age showed no

polyps in 2,413 examinations[17] and one in 500 examinations.[6] One to 3 per cent of patients subjected to gastroscopic examination have gastric polyps.[11, 19]

Age and Sex Incidence.—The age range of patients in our group was from 17 to 81 years with the average age 64.7 years. There were fifty-nine men and thirty-eight women.

DIAGNOSIS

Symptomatology (see Table II).—

Benign polyps (69 cases):

SYMPTOMATIC PATIENTS.—The symptoms found in the sixty-nine patients with benign lesions were recorded separately from those with carcinoma. Thirty-eight patients had gastric symptoms.

TABLE II

SYMPTOMS	BENIGN SINGLE OR DOUBLE ADENOMAS (48)	MULTIPLE ADENOMAS (21)	MALIGNANCY (28 CASES)
Epigastric distress	17	11	21
Nausea and vomiting	6	3	6
Diarrhea and/or constipation	4	4	2
Significant weight loss	4	0	15
Anemia:			
Pernicious	11	2	3
Hypochromic	0*	2	3
Bleeding:			
Melena	1*	0	4
Hematemesis	0*	0	1
Asymptomatic	25†	6	1

*One patient with bleeding from Banti's syndrome was omitted.

†Includes seven patients with pernicious anemia but otherwise no symptoms pointing to gastric pathology.

Epigastric distress of some type was found in twenty-eight of the sixty-nine cases in this group. Indigestion, gaseousness, or epigastric fullness usually most marked after eating were the usual complaints. A dull aching epigastric pain less well localized than that of a duodenal ulcer and less frequently relieved by antacids, milk, and cream, was common.

Nausea and vomiting were experienced by nine patients. In none of this group were these symptoms severe.

Diarrhea and constipation were each listed as present in four patients.

Loss of weight was a prominent feature in only four of the sixty-six patients where other known pathology did not account for it. Two of these four patients had polyps prolapsing into the duodenum.

Bleeding had been noted by only three of our patients and had not been a prominent symptom in any case.

Anemia was a frequent finding. While hypochromic iron deficiency anemia was encountered in only three patients, thirteen of our patients with benign polyps had pernicious anemia diagnosed prior to or at the time of the diagnosis of polyps. A hyperchromic anemia with bone marrow findings typical of a primary anemia developed within two years after gastric resection in two of the three patients mentioned as having hypochromic anemia.

ASYMPTOMATIC PATIENTS.—Twenty-four of the sixty-nine patients had no symptoms referable to the stomach. An additional seven patients had only the diagnosis of pernicious anemia to indicate gastric disease. Combining these two groups we find thirty-one of sixty-nine patients are completely asymptomatic.

Malignant Polyps and Polyps Associated With Malignancy (28 cases):

As would be expected, the symptomatology in this group was more severe than in the group with benign polyps and adenomas.

Epigastric distress was present in twenty-one of twenty-eight patients. In many of the patients anorexia and increased discomfort after eating were noted. In all the cases the severity of the distress was such as to call attention to the stomach as the seat of pathology.

Nausea and vomiting had been experienced by six patients, one of whom had hematemesis.

Weight loss of a degree calling it to the patient's attention was present in sixteen patients. Weakness was also a frequent complaint.

Anemia of the hypochromic iron deficiency type usually ascribed to blood loss and pernicious anemia were each noted in three cases.

Bleeding manifested by melena was present in four patients and hematemesis in one.

LABORATORY FINDINGS

Benign Polyps.—

Stools were examined by the guaiac test in thirty-six cases and were positive in nine.

Gastric analysis using histamine as a stimulus was performed in sixty-seven of the sixty-nine patients having benign polyps. Fifty-nine of the sixty-seven patients were achlorhydric, five had free acid of less than 30°, associated with a low value for combined acid, and three patients had acid in the normal range. All three of these patients had single polyps. Thirty-five of the patients had two or more gastric analyses.

Malignant Polyps and Polyps Associated With Malignancy.—

Stool examinations by the guaiac test were made in twenty-one patients with malignancy. Positive tests were obtained in seventeen cases.

Gastric analyses were performed in twenty-three patients. Achlorhydria was found in twenty-two. One patient had 4°, 6°, 6° of free acid in the three specimens after histamine stimulation.

ROENTGENOLOGIC EXAMINATION

The barium contrast roentgen examination of the stomach is the most important single method of detection of polyps (Fig. 1). Its widespread use for minimal symptoms or as part of a complete routine examination accounts for the discovery of most of the polyps giving minimal or no symptoms. The examiner should use precautions to make a preliminary examination with only a small amount of barium in the stomach and, by pressure, to bring out the

detailed mucosal pattern. Where small lesions are detected or suspected, examinations using air contrast methods similar to those applied in the detection of colonic polyps (Fig. 2) are extremely useful.[9, 15, 16, 21]

In twenty of these ninety-seven cases the cancer overshadowed the polyps. The roentgenologist was able to see the polyps in seventy of the residual seventy-seven cases. In twenty-seven cases there was doubt as to the benignancy or malignancy of the lesions. This doubt was deemed present in those cases where the examiner stated the diagnosis as probable or possible malignancy, where the gastroscopist disagreed with the diagnosis, or where malignancy was proved later. Eleven of these twenty-seven cases had malignant polyps. The roentgenologist called eight malignant and three benign. Two of the lesions called benign had correction of this diagnosis, nine and nineteen months later, when the lesions were still operable. The third patient had a positive biopsy of a cervical node after three years' follow-up. Sixteen cases with benign polyps fell into this controversial group. The roentgenologist called ten possibly malignant, five benign, and failed to see one.

Fig. 1.—Roentgenogram showing multiple adenomas.

GASTROSCOPIC EXAMINATION

Gastroscopy is an invaluable aid in diagnosing the presence of benign lesions of the gastric mucosa. The differentiation of small benign polyps from polypoid hyperplasia is best made by gastroscopy. Gastroscopically, benign polyps appear as small flat domes like split peas, small teats, or mushrooms. The mucosa which covers the polyps appears normal, and is smooth, not nodular. These tumors are sharply demarcated from the surrounding mucosa which usually appears normal. The finding of atrophic mucosa in the stomach suggests that the tumor is an adenoma. The pseudopolyps are "large sponge-like, bluish-red protrusions of a terribly swollen hypertrophic mucosa."[20] The

gastroscopic finding of an uneven, nodular, sessile polyp suggests malignancy, especially if the mucosa covering the polyp has whitish cobweblike streaks.

Gastroscopic examination was made in seventy cases. The lesion was seen in fifty-nine. In the majority of the cases the lesions were obviously benign or malignant, while twenty cases were doubtful. Four of the seven malignant cases were so diagnosed. One of these diagnostic errors was corrected six months later. Thirteen of the twenty doubtful cases were benign. Ten of these were called possibly malignant, two benign, and in one the lesion was not seen.

Fig. 2.—Air-contrast roentgenogram of stomach shown in Fig. 1.

The diagnosis of the precise nature of a gastric polyp is difficult. In our clinic we followed the practice of recommending removal of these lesions if either the gastroscopist or roentgenologist thought the lesions malignant. The lack of definite evidence of malignancy caused delay in operation in three patients. A summary of the pertinent information regarding these patients follows:

CASE 1.—A. M., a 76-year-old woman, had a diagnosis of probable malignancy of a gastric polyp by the gastroscopist after her primary examination. The roentgenologist thought the polyp benign. A recommendation of a gastric resection was not accepted by the patient. At re-examination nine months later the roentgenologist agreed that malignancy was probable. The force of this additional evidence allowed the clinician to secure permission for removal of the lesion. The lesion was a polypoid carcinoma, no lymph nodes were involved, and the patient is alive and well three years and five months after operation.

CASE 2.—A. T., a 79-year-old woman, had polyposis diagnosed by both methods. Six months later one of the lesions was thought malignant by the gastroscopist. Thirteen months later the roentgenologist agreed that malignancy was present. A polypoid carcinoma 3.5 by

3.5 by 2 cm. in diameter with positive lymph nodes was resected nineteen months after the initial examination. The patient was alive one year and seven months later but was thought to have carcinomatosis.

CASE 3.—N. J., a 46-year-old man, when first seen in 1942 stated that he had had a feeling of nausea and abdominal discomfort each morning about four or five o'clock, just after arising. This was relieved by vomiting, but recurrence after drinking coffee with cream was common. The pertinent features of his examination were an achlorhydria on gastric analysis on April 4 and 7, 1942. The latter examination was made with three injections of 0.5 mg. histamine hydrochloride given subcutaneously at one-half hour intervals. A single stool examination showed no occult blood. Barium roentgen study of the upper gastrointestinal tract showed no pathology. No therapy was prescribed.

The patient returned in August, 1945, when gastric roentgenography showed a polypoid defect on the greater curvature of the stomach. Gastroscopic examination failed to confirm this finding. The gastroscopist saw the stomach well and noted a slight pallor in the preantral area as well as some evidence of mucosal atrophy. Re-examination by the radiologist in March of 1946, May of 1947, December of 1947, and April of 1948 showed changes in the area noted. These looked more and more like enlarged folds but the diagnosis of polyps was never completely discarded until a left supraclavicular node was discovered in August of 1948. A diagnosis of carcinomatous metastases from a carcinoma of the stomach was then made. The patient died in December of 1948, three years and eight months after the gatsric lesion was first noted.

SUMMARY OF DIAGNOSIS

As noted earlier we have observed seventy-seven patients in whom the problem of differentiating carcinoma from benign polyps was the primary consideration. The three cases just cited constitute those in which an original diagnosis of benign polyps was eventually changed to cancer. In Case 1 (A. M.) the diagnosis of carcinoma by the gastroscopist was probably correct. In Case 2 (A. T.) both the gastroscopist and roentgenologist thought the polyps were benign. The gastroscopist six months later stated "the lower polyp lying at the level of the angulus on the posterior wall toward the greater curvature has undergone a definite change since the last examination. It has become larger and developed a cauliflower-like appearance. The base is broader and there is definite suggestion of involvement of the mucosa about the base by an infiltrative process. Impression: "Malignant degeneration of a gastric polyp."

In Case 3 (N. J.) it is improbable that an adenoma or any polypoid lesion was present, since no polyps were visible by the gastroscopist who saw the area in question, and after his first two examinations the radiologist believed the change due to enlarged gastric-folds and finally to cancer.

Thus we find that in seventy-seven patients for whom we advocated resection of all polyps suspected of being malignant by either the roentgenologist or the gastroscopist, only three patients had delay in treatment of carcinomas. In one of these cases it is probable that malignant degeneration of a benign polyp occurred.

PATHOLOGY

All nonepithelial polyps were excluded from this series when their true nature became apparent. The majority of the adenomas studied had the

morphology of those in Menetrier's polyadenoma polypeux group.[10] There was considerable variation in their size and configuration. Minimal adenoma formation consisted only of a local overgrowth of glands with the resultant thickening of the mucosa or the appearance of an area of hyperplasia (Fig. 3). A second step in the development apparently was the result of crowding of the hypertrophied glandular epithelium superficial to the muscularis mucosa which resisted stretching. The consequent buckling of the mucosa resulted in the beginning of a pedicle. The formation of a long pedicle was usually dependent on the effect of the force of peristalsis on the adenoma. We noted no difference in appearance between the adenomas occurring alone and those where

Fig. 3.—Roll section showing atrophic gastritis with areas of hyperplasia and beginning polyp formation.

several or even fifty occurred in a specimen. In the latter specimens all gradations from sessile to definitely pedicled adenomas were frequently noted (Fig. 4). The tumors rose abruptly from the surrounding mucosa and were sharply demarcated from it. The benign lesions were soft, smooth, often finely lobulated, and freely movable on the underlying muscularis. Malignant change was suggested by large size, fixation of the growth to the underlying wall, and especially by thickening and infiltration of that wall. The malignant tumors showed a coarser cobbling of their surface and most of them were sessile, though some had short pedicles.

Histology.—

Microscopically there was no difference between the pathology in the single and the multiple adenomas. The epithelium was arranged in well-formed glands which were elongated, frequently branched, and anastomosed

with other glands: The glands ran in various directions with no definite orientation with respect to the muscularis mucosa (Fig. 5).

Cell Type.—The cells were usually large cylindric mucous cells which contained either round or oval nuclei situated near the basement membrane. The supranuclear part of the cell was either a goblet cell bulging with mucus or had the reticular structure of the mucous cell (Fig. 6). Cysts were frequently present, usually filled with mucus (Fig. 5).

A second type of epithelium composed of cuboidal cells with round centrally located nuclei was seen. The cytoplasm of these cells was pale and had a fine granulation. These cells formed simple tubular glands smaller than those composed of mucous cells.

Fig. 4.—Photograph showing adenomas in various stages of development.

A third type of epithelial cells was encountered. These cells were found adjacent to and intermixed with the mucous cells. The large cylindric cells had a darkly staining cytoplasm showing no evidence of mucus formation. The nuclei were centrally placed, elongated, hyperchromic, and contained an increased amount of chromatin. The nuclei more than half filled the cells. More mitosis was present than in the other types of cell. The glands formed by this type of cell were less regular and branched more frequently than those of preceding groups. Frequently the change from the mucous type cell to this anaplastic type occurred abruptly. Adjacent glands or even cells in a

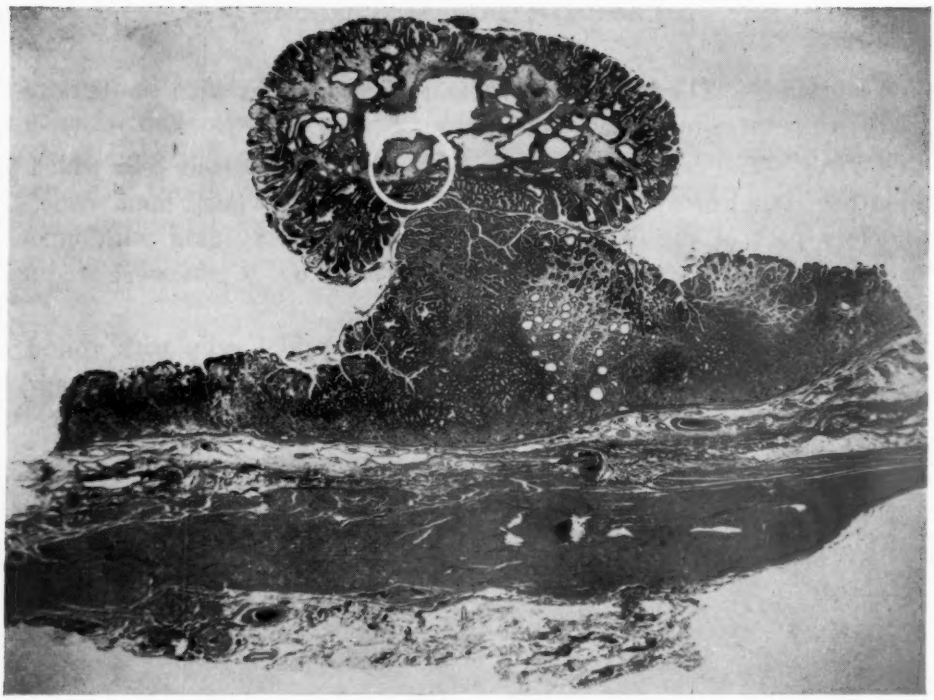

Fig. 5.—Enlargement of adenoma showing pedicle and cyst formation.

Fig. 6.—Photomicrograph showing the usual mucous-type gland

single tubule were often of these two different cell types (Fig. 7). This change was called "anaplasia."

Finally, those glands and cells showing malignancy were encountered. The cells were large and cylindric in shape. Their cytoplasm was granular and hyperchromic. The nuclei were enlarged to occupy over two-thirds of the cell and there was an increased amount of chromatin present. Some cells were found growing independently in the supporting parenchyma of the stalk of the adenoma. In some of the adenomas these active-appearing glandular elements were found growing in the muscularis mucosa or penetrating this layer and invading the muscular layer of the wall. Cell morphology alone was not regarded as sufficient evidence to indicate malignant change.

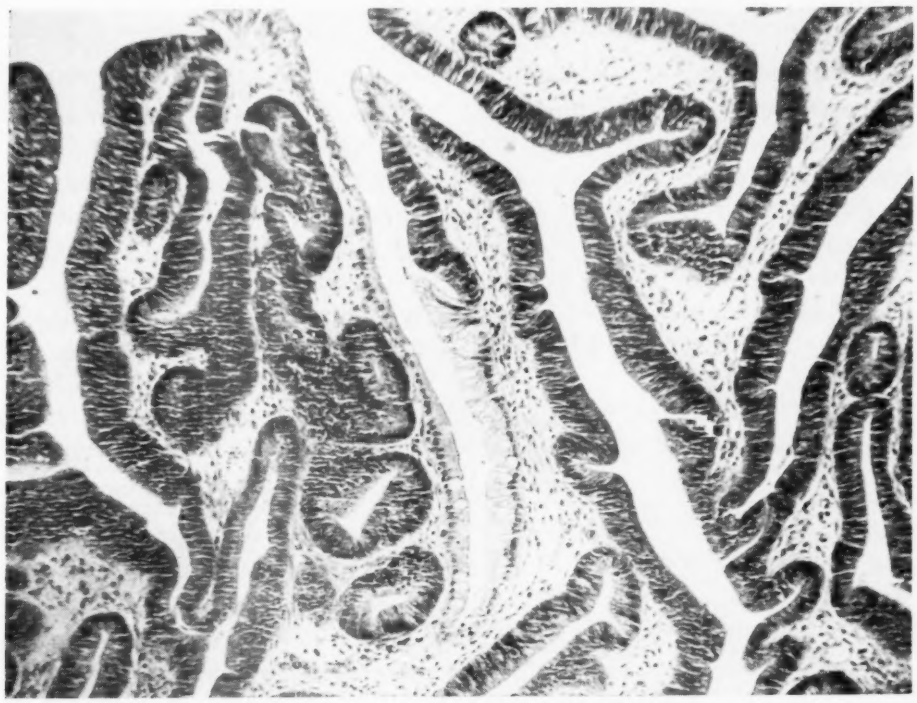

Fig. 7.—Photomicrograph showing the change called anaplasia.

No attempt was made to separate adenomas composed of the first two types of cells, as most formations contained both types. The large mucus containing cylindric cells was encountered in the more superficial part of the adenoma and the smaller cuboidal pyloric gland cells were present in the deeper tissues nearer the muscularis mucosa.

Search was made in all adenomas for areas of anaplasia. Tissue was available for study in fifty-seven of the fifty-eight cases where operations were performed. Fifty-four cases were of the polyadenoma polypeux type. Table III shows the incidence of anaplastic change in these adenomas. The high incidence of the anaplastic cell type in the adenomas associated with malignancy will be noted.

TABLE III

TYPE	NUMBER OF CASES	ANAPLASIA		NOT DETERMINED
		PRESENT	ABSENT	
Malignant adenomas and adenomas associated with carcinoma	25	13	10	2
Benign adenomatosis	8	2	4	2
Single benign adenomas	21	3	16	2

The lesions were separated into groups according to size. The size of the lesion was noted in all eighteen cases showing anaplasia. There were four adenomas less than 1 cm., seven 1 to 2 cm., and seven more than 2 cm. in diameter. The sizes were known in twenty-nine of the thirty adenomas not showing anaplasia. Twenty were less than 1 cm., six from 1 to 2 cm., and three were more than 2 cm. in diameter.

Polyadenoma en Nappe.—Three adenomas conforming to Menetrier's polyadenoma en nappe were encountered.[10] The lesion was a raised, well-demarcated plaque composed of closely placed glands. There was very little connective tissue hypertrophy. The growth was apparently in the fundus of the gland and resulted in rows of elongated gland tubules which branched and anastomosed only infrequently. The cells forming this type of adenoma were cylindric with oval or round nuclei. The cytoplasm was granular and there was no evidence of mucus formation. Two lesions had areas of definite malignant change, and the third was found in a stomach with a carcinoma.

TABLE IV. SIZE OF POLYPS

GROUP	LESION	NO. OF PATIENTS	LESS THAN 1 CM.	1 TO 2 CM.	2 CM. OR OVER
1	Multiple benign	11	8	3	
2	Single benign	26	17	8	1
3	Multiple associated with cancer	(11) 9†	7	2	0
4	Multiple (resected)	(10) 8*	2	5	1
5	Single (resected)	15	6	7	2
6	Single (polypectomy)	7	6	1	
7	Single associated with cancer	(17) 12	5	4	3
	Total		51	30	7

*Size of two lesions not determined.

†Two patients were omitted from Group 3 because of questionable malignancy in associated adenomas. Likewise five were omitted from Group 7 because of malignancy in the lesion.

Size.—The size of benign adenomas was determined in eighty-eight of our ninety-seven cases. In two of the nine cases not shown the specimen was unavailable and a definite measurement of size was not in the record. Seven cases having malignancy in the polypoid lesions were excluded. In cases having multiple lesions the measurement of the largest benign lesion was used. Table IV indicates that fifty-one patients had lesions less than 1 cm., thirty had lesions 1 to 2 cm., and seven had lesions larger than 2 cm. in diameter. Six of the seven lesions excluded from the above group because of malignant change were over 2 cm. in diameter. We have a total of thirteen lesions in this size group. The seven benign lesions were 2.5, 2.5, 2.5, 3, 4, 5, and 8 cm.

in diameter. The six malignant ones, 2.5, 3, 6, 6, 8, and 10 cm. in diameter. Only one malignant lesion was less than 2 cm. in diameter.

Location.—The localization of polyps was tabulated for all cases (Table V). Inaccuracies of location resulting from the shortcomings of the methods of examination are undoubtedly present. Gastroscopically the lesser curvature of the antrum, posterior wall of the body, and most of the cardia are blind spots. Roentgenologically, lesions of the cardia are diagnosed with less accuracy because of the difficulty of applying pressure. Likewise where resection by the closed technique or polypectomy is performed small lesions may remain in residual portions of the stomach which are undetected by palpation.

TABLE V. LOCATION OF POLYPS

GROUP		NUMBER	ANTRUM	BODY	CARDIA	GENERAL
1	Polyposis (clinical diagnosis)	11	1	5	1	4
3	Adenomatosis with cancer	11	3	5		3
4	Adenomatosis operated and	10	1	6	1	2
	Benign	32	5	16	2	9
2	Single polyps (clinical diagnosis)	26	14	9	3	
7	Single adenomas with cancer	17	4	13		
5 and 6	Single adenomas operated and	22	13	9		
	Benign	65	31	31	3	
	Total	97	36	47	5	9

In fifty of the fifty-eight cases operated upon sufficient mucosa was present on the specimen to determine the characteristics of the mucosa. Forty-eight specimens showed a moderate to marked atrophy. In two cases a normal mucosa was found. Both of these patients had single adenomas and had free hydrochloric acid on gastric analysis.

ETIOLOGY

Atrophic Gastritis.—An irritation due to chronic inflammation leading to chronic atrophic gastritis has been the most commonly advanced theory of pathogenesis of adenomas of the gastric mucosa.[7, 10] Certainly our finding of atrophic gastritis of a moderate to marked severity in forty-eight of the fifty cases suggests more than a coincidental relationship. The high incidence of achlorhydria and the finding of atrophic gastritis in fifty-two of sixty-four patients on gastroscopic examination corroborates this relationship. In general it has been assumed that the atrophic gastritis preceded the development of the adenomas. In thirteen instances in this series we were able to show evidence that mucosal disease was present prior to the development of the adenomas (Table VI). Superficial gastritis was noted in seven of the sixty-four cases. In four of the seven, superficial gastritis and atrophy were found in the same stomach. Schindler states that the transition of superficial gastritis to atrophic gastritis has been observed frequently enough to establish, in his opinion, a causal relationship.

Experimental Gastritis and Polyps.—Fibiger, 1913, injected rats' stomachs with a nematode parasite of the cockroach. These animals developed polyps of the forestomach which has a squamous epithelial lining. Since similar

TABLE VI

ACHLORHYDRIA DIAGNOSED	PERNICIOUS ANEMIA DIAGNOSED	NEGATIVE GASTROSCOPY	NEGATIVE ROENTGENOGRAM	GASTROSCOPIC DIAGNOSIS OF LESION	ROENTGENOLOGICAL DIAGNOSIS OF LESION	INTERVAL BETWEEN DIAGNOSIS AND APPEARANCE OF LESION (YEARS)	
						FOR ACHLORHYDRIA	FOR ROENTGEN DIAGNOSIS
1. 1936	1936	—	1946	1947	1947	11	1
2. 1935	1942	1944—Atrophy	1935	—	1943	8	8
3. 1942	—	—	1942	1945	1945	3	3
4. 1942	—	—	1942	1948	1947	5	5
5. 1935	1935	—	1936	1942	1942	7	6
6. 1936	—	—	1936	—	1949	13	13
7. 1940	—	—	1946	—	1947	7	1
8. 1936	1936	—	1936	1940	1940	4	4
9. 1936	1939	1936—Atrophy	1936	1939	—	3	3
10. 1940	—	1940—Atrophy	1940	1944	1944	4	4
11. 1937	—	—	1937	1943	1943	6	6
12. 1942	—	—	1942	—	1946	4	4
13. 1940	—	1940—Superficial gastritis	—	—	1946	6	6

tumors may occur after rats have eaten a deficient diet, the precise effect of the parasites is difficult to determine. Stewart produced hyperplastic and neoplastic lesions in the stomach of mice by local implantation of a carcinogen, and local tumor growths resembling adenomas have been noted after the local application of carcinogenic substances. Strong was able to develop gastric adenomas regularly, by using inbred C_3H mice. He administered carcinogens by injecting methylcholanthrene in sesame oil subcutaneously into 60-day-old mice. Some of the mice developed gastric adenomas and possible carcinomas. By selecting susceptible animals as breeders he was able to develop a stock which regularly developed benign or possibly malignant adenomas of the glandular stomach. This illustrates the effect of carcinogen on a suitable genetic substrate and suggests that both hereditary and chronic irritative factors may be important.[24]

Heredity.—The hereditary thesis for the development of gastric polyps was advanced by Wechselman. The participation of the stomach in widespread gastrointestinal polyposis, a condition in which a familial character can often be shown to be present, seems the most tangible evidence of the influence of heredity on the development of adenomatosis (polyposis) of the stomach. The rather advanced age of the majority of patients when the diagnosis is established clinically and the extreme rarity of the diagnosis in children even in autopsy material[8, 23] are evidence against the congenital origin of the majority of cases.

Pernicious Anemia.—The frequency of development of gastric adenomas in pernicious anemia patients[18] where a severe atrophic gastritis is always present, suggests a precursor role for atrophic gastritis or that these two pathologic changes may have a common etiology. Since the hereditary predisposition to pernicious anemia is generally accepted[5] the assumption of predisposition to gastric adenomas follows.

Atrophic Gastritis.—Chronic atrophic gastritis per se has frequently been indicated as a precursor of or having a common origin with adenomata.

The hereditary character of chronic atrophic gastritis is suggested by the increased frequency of achlorhydria in relatives of achlorhydric and especially of pernicious anemia patients.[1]

PROGNOSIS

Benign Polyps.—Many patients diagnosed as having benign polyps were observed without operation. Such patients were regarded as having benign polyps. In order to minimize the possibility of an erroneous diagnosis of a benign polyp where a malignancy actually existed only patients observed for one or more years were included in calculating the period of observation. Only one patient (N. J.) with malignancy was observed for more than one year before the malignant nature of the lesion was suspected to a degree leading to a recommendation of exploration.

Single or Double Polyps.—

Nonoperative treatment resulted in observing twenty-six patients with single polyps for periods of one to nine years with an average of 3.7 years. Two patients had cancer. One of these (N. J.) died of cancer without a resection. The second had a gastric resection and survives at three years and five months without recurrence (Table VII).

TABLE VII. RESULTS OF NONOPERATIVE THERAPY FOR POLYPS OF THE STOMACH

NUMBER OF POLYPS	NUMBER OF PATIENTS	AVERAGE DURATION OF FOLLOW-UP IN YEARS	NUMBER OF PATIENTS DEVELOPING CANCER
Single	26	3.7	2
Multiple	11	4.2	1

Operative treatment of a total of twenty-two patients with single or double gastric adenomas was carried out. Fifteen patients had their adenomas removed by gastric resection with one death. Three patients died during the first postoperative year of unrelated causes. The remaining eleven have been followed from one to ten years for an average of 4.4 years. None has developed either new polyps or cancer (Table VIII).

TABLE VIII. RESULTS OF OPERATIVE THERAPY IN PATIENTS WITH A SOLITARY GASTRIC POLYP

TYPE OF OPERATIVE PROCEDURES	NUMBER OF PATIENTS	MORTALITY RATE	NUMBER OF PATIENTS DEVELOPING NEW POLYPS	NUMBER OF PATIENTS DEVELOPING CANCER
Subtotal gastric resection	15	1	0	0
Polypectomy	7	0	2	0

Seven patients with single adenomas were treated by polypectomy (Table VIII) as were two with multiple adenomas. Two of the seven patients with single adenomas had new or residual polyps detected postoperatively. These have been followed for two and eight years without significant change. The two patients having polypectomy (Table IX) for multiple adenomas have had

TABLE IX. RESULTS OF OPERATIVE THERAPY IN PATIENTS WITH MULTIPLE POLYPS

TYPE OF OPERATIVE PROCEDURES	NUMBER OF PATIENTS	MORTALITY RATE	NUMBER OF PATIENTS DEVELOPING NEW POLYPS	NUMBER OF PATIENTS DEVELOPING CANCER
Subtotal gastric resection	9	0	3	1
Polypectomy	2	0	2	0

residual polyps for periods of ten and fifteen years with no significant change in the polyps or gastric cancer developing.

Polyposis.—

Nonoperative treatment was carried out on eleven patients with polyposis. The period of observation ranged from one to ten years and averaged 4.2 years. One patient (A. T.) developed a cancer (Table VII).

Operative treatment by gastric resection was performed on eight patients with multiple adenomas without operative death (Table IX). Four of these patients had been observed preoperatively for an average of 7.4 years. Four patients having residual polyps have been observed for an average of three years after operation. One of these (O. F.) developed an inoperable cancer in the gastric pouch four years after resection.

TREATMENT

There has been considerable controversy over the treatment of polypoid lesions of the stomach. The difference of opinion is centered about the incidence of malignancy in polyps. Review of the literature shows that from 9 to 40 per cent of polypoid lesions are malignant.[3, 21]

It is well to remember that nearly all these cases were symptomatic and the lesions were usually very large. Rieniets and Broders have pointed out the correlation between the size of adenomas and their likelihood of being malignant. They noted that the average volume of the seventy-four benign lesions encountered at autopsy was 0.69 c.c. while the average size of twenty malignant lesions removed at operation was 19.67 c.c.[14]

In our clinical material only one of eighty-two adenomas less than 2 cm. in diameter was malignant. Six of thirteen lesions larger than 2 cm. in diameter were malignant. As a result of these observations we have accepted the following plan of therapy:

Nonoperative Treatment.—The nonoperative or observation type of management is recommended in asymptomatic or mildly symptomatic patients with polyps less than 2 cm. in diameter which appear benign to the gastroscopist and roentgenologist. These patients are observed by roentgenologic and gastroscopic examination every three or four months for the first year and then biannually. The development of severe symptoms from prolapse or bleeding is an indication for operation. The probability of malignancy as indicated by an increase in size of the lesion, infiltration of the gastric wall, or increased nodularity and pallor of the surface of the lesion indicates the need for operative treatment.

Operative Treatment.—The following groups of patients should be subjected to operation: (1) patients with polyps larger than 2 cm. in diameter, (2) patients with polyps smaller than 2 cm. in diameter in which the roentgenologist or gastroscopist suspects malignancy, (3) patients with clinical symptoms due to polyps if the symptoms are of a severity to justify the risk of operative intervention and (4) patients who refuse or are unable to accept adequate observation because of geographic or personal reasons.

Subtotal gastric resection:

The resection of 75 to 85 per cent of the stomach is recommended as the routine operation where surgery is indicated.

Single tumors of the body and antrum having the characteristics of polyps and accompanied by achlorhydria and/or mucosal atrophy are regarded as potentially malignant but in addition are regarded as being a sign of atrophic gastritis with its probable inclination to further polyp formation and malignant degeneration. Subtotal gastric resection is recommended even for single lesions when accompanied by achlorhydria or mucosal atrophy. Most of these lesions are adenomas and a gastric resection removes adjacent atrophic mucosa and undetected adenomas with their malignant potential and provides an adequate cancer operation where malignancy is present.

The one major exception to this routine has been in patients having a polyp in the cardia. In these individuals an anterior gastrotomy is made and the lesion removed. The lesion is subjected to immediate "frozen section" and histologic examination. If the lesion is benign and solitary, polypectomy with removal of a rim of mucosa about the base is performed. If the lesion of the cardia is malignant a total gastrectomy including the lesser and greater omentum and a splenectomy is indicated.

Multiple adenomas confined to the antrum and body of the stomach demand a subtotal gastric resection. Since lesions of the cardia are difficult to diagnose, an anterior gastrotomy and inspection of the interior of this region is recommended. This allows one to include adjacent previously undetected lesions in the resected specimen. If a single adenoma is detected it may be dealt with as previously outlined under therapy for single lesions of the cardia. If multiple lesions are present in the cardia a total gastrectomy is indicated.

DISCUSSION

The predominance of epithelial tumors in gastric malignancies magnifies the importance of their precursor lesions. Epithelial polyps, which we have designated "adenomas," and pernicious anemia are two such recognized lesions. Whereas a definite clinical diagnosis of an adenoma rather than a polyp of mesenchymal origin is not always possible, it is important that histologically identified adenomas be separated from other polypoid lesions if their preoperative diagnosis is to be possible and if their true potentiality for malignant degeneration is to be documented.

It is impossible to determine what fraction of gastric cancer originates from adenomas. The incidence of adenomas is small. There are a number

of conditions where the incidence of gastric adenomas is increased. Careful examination of pernicious anemia patients reveals about a 5 or 6 per cent incidence of gastric polyps. Similarly achlorhydric patients show 3 per cent and hypochlordric patients about 1 per cent of gastric polyps. Our finding of atrophic gastritis in forty-eight of fifty patients having gastric adenomas indicates the frequency of this association. Since the diagnosis of atrophic gastritis can be made only histologically or gastroscopically, this association loses much of its value as a method of selection of patients for inclusion in a productive survey. The presence of achlorhydria and probably hypochlorhydria suggests that roentgenographic or gastroscopic examination is necessary for detection of gastric adenomas. Eighty-five per cent of our patients were achlorhydric and less than 5 per cent had a normal gastric acidity. Fifty-six cases of gastric adenomas were taken from the literature and fifty of these were achlorhydric.

Two patients with achlorhydria, hypochromic anemia, and no history of either hematemesis or melena had gastric resection performed. A severe atrophic gastritis was found on pathologic examination of their stomachs. Both of these patients developed pernicious anemia within two years after resection. It is difficult to determine how much the partial gastric resection contributed to the development of the pernicious anemia. The rarity of the development of pernicious anemia after gastric resection for duodenal ulcer suggests that the underlying pathology, i.e., atrophic gastritis, was a more important factor than the operation.

The roentgen study of the barium-filled stomach is the most important single method of detecting gastric polyps because it is so widely available and easily applied. The differentiation of gastric polyps and hypertrophic gastric rugae by roentgen methods is difficult.

Gastroscopy is an essential part of the diagnostic routine where gastric polyps are suspected. Small lesions undetected by the roentgenologist can frequently be seen gastroscopically. A stomach in which only one or two polyps has been noted will often reveal additional polyps when examined gastroscopically. This method also makes it possible to differentiate between gastric polyps and hypertrophic gastritis, and to diagnose atrophic gastritis. Rigler has advocated the periodic roentgen examination of the stomach of patients with pernicious anemia. The frequency of occurrence of polyps and carcinoma in patients with pernicious anemia indicates that gastroscopy should be part of the routine examination of these patients.

Almost all of the polyps were the mucous adenoma of Menetrier's polyadenoma type. The common association of an atrophic gastritis with adenomas indicates that these lesions are etiologically related.

The size of gastric adenomas seems to be the best criterion of their malignancy. In determining the size, the carcinomas were omitted unless only a single polypoid malignant lesion was present. The size of the largest adenoma in each case was used. Only a single lesion of the eighty-two which were less than 2 cm. in diameter was found to be malignant. Six of

thirteen from 2.5 to 8 cm. in diameter were malignant. This striking difference was at first difficult to accept. Twenty-six cases of malignant adenomas from the literature, which were selected only by taking those whose size was stated, revealed no lesion less than 2 cm. in diameter. Only five lesions were from 2 to 5 cm. and twenty-one were larger than 5 cm. in diameter. It is difficult to understand why more small lesions did not show malignancy. The frequent finding of benign areas in malignant lesions suggests that the malignant polyps began as benign lesions which have undergone malignant degeneration. Undoubtedly this occurs, although observation of an apparently benign lesion which later was shown to be malignant has seldom been attained. We have made one such observation, but the time interval between the diagnosis of a benign lesion and the change to a malignancy was only six months. The fact that there were many other benign adenomas in the stomach lends credence to the carcinomatous degeneration of this benign lesion. Our observation of forty-one patients with benign-appearing adenomas for average periods of nearly four years indicates that malignant change is less common than was once supposed.

Intimately related to the development of malignancy in a benign polyp, and probably of equal importance, is the development of carcinoma in these stomachs at a site away from the polyp. This is indicated by the patchy hyperplastic change of the generally atrophic mucosa so frequently demonstrable on gross and microscopic examination of resected specimens of patients with multiple lesions (Fig. 3), as well as by the finding of nonpolypoid infiltrative carcinomas.

Our recommendations of subtotal or total gastrectomy are based on this knowledge and the presumption that atrophic gastritis predisposes to carcinomatous change. They would not be pertinent where a normal acidity and mucosa were present since polyps found under these circumstances would include mostly mesenchymal tumors. Removal of such single benign lesions by polypectomy is good treatment.

The recommendation of a subtotal gastrectomy for patients with multiple polyps may be too conservative. Four of eight patients so treated had residual or new polyps and one of these developed an inoperable cancer in the residual pouch. The addition of an anterior gastrotomy which permits inspection of the gastric pouch should obviate leaving polyps. If further experience indicates that either new polyps or carcinomas develop in the residual stomach with a frequency which justifies total gastrectomy, we will adopt the procedure.

The recommendation of the nonoperative or observation management of benign polyps evokes thought and discussion. The increased incidence of carcinoma in stomachs bearing polyps is established. Our experience indicates that the probability of carcinomatous change in the small, benign-appearing lesions is small. Further experience may show that certain groups, for example, pernicious anemia patients with polyps or patients with multiple polyps, have an incidence of carcinoma large enough to indicate routine subtotal or

even total gastrectomy. Most asymptomatic polyps are discovered during a complete examination for various infirmities afflicting patients with an average age of sixty-four years. Therefore, many factors must be considered in selecting operative or observation management of a patient. The knowledge of the frequency of malignant change is the essential prerequisite of a sound decision.

CONCLUSIONS

1. Thirty-one of sixty-nine patients with benign gastric adenomas were asymptomatic. Only one of twenty-eight patients with a malignancy was asymptomatic.

2. Achlorhydria is present in 85 to 90 per cent of patients with gastric adenomas. Gastric analysis is a satisfactory screening test for the selection of patients for roentgenologic and gastroscopic examination for gastric adenomas.

3. Most gastric adenomas occur in association with a chronic atrophic gastritis. There is no difference in the gross histologic morphology of adenomas occurring singly or in adenomatosis.

4. Subtotal gastric resection performed in patients with benign adenomas and a severe atrophic gastritis may be followed by pernicious anemia.

5. Anaplastic changes appear to be more common in the cells of the adenomas associated with and containing malignancy than in those where no malignancy exists.

6. Small gastric adenomas are much less likely to be malignant than large ones. The size of adenomas is probably the most valid single criterion for determining malignancy.

7. Carcinomatous degeneration of benign adenomas does occur. The development of carcinoma in other parts of adenoma-bearing stomachs may be of as great importance as degeneration of benign polyps.

8. The occurrence of malignancy in the presence of small polyps diagnosed as benign is less frequent than was formerly supposed.

9. Observation management of patients diagnosed as having small benign lesions is justified if they can be observed at frequent intervals.

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

FRANK H. HAMILTON, M.D.

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FRANK H. Hamilton (1813-1886) belonged to the generation of surgeons who saw the most rapid changes in the history of surgery. When he began his career, Philip Physick, "Father of American Surgery," pupil of John Hunter, was still alive and surgery was not materially changed from that of Hunter. Pain was the inevitable accompaniment of every operation and suppuration was a normal consequence of surgery. By the close of Hamilton's career, methods for overcoming these overwhelming disadvantages of operations were established and surgery was progressing to the stage of the deliberate, carefully planned operation; perhaps it is symbolic of this change that one of Hamilton's last interns was William Halsted.

Hamilton was born in Vermont in 1813 where his father was both a farmer and a stage coach operator. Early in his life, the family moved to Schenectady and Hamilton attended Union College. His medical education was fairly typical of the period. It began with a preceptorship in the office of an Auburn, N. Y., physician, whose position as a prison doctor gave him an enviable amount of anatomic material. This was followed by a lecture course at the Fairfield Medical School, which gave him a license to practice medicine, but he continued to study and in 1835, after a second lecture course, he received an M.D. degree from the University of Pennsylvania. When he returned to Auburn, he gave a private course in anatomy and surgery which must have been a considerable success because in 1839, at the age of twenty-six, he became Professor of Surgery at Fairfield and, a year later, Professor of Surgery at the Geneva Medical School. This latter appointment was commented upon by the Boston Medical and Surgical Journal as being a well-merited appointment which was a welcome deviation from "the monstrous and glaring iniquity of putting cousins, nephews, and almost aunts into chairs which it is not possible for them to sustain with dignity or profit to the world." For the next five years, Hamilton lived in Rochester, N. Y., and held classes at Geneva. In 1845, he made an extensive trip to Europe visiting the great hospitals of London, Paris, and other cities which he later described in articles in the Buffalo Medical Journal. His notes on this trip indicated that in Paris he watched Roux operate on a neck tumor and heard him discuss air embolism. He watched Velpeau operate for open cancer on cases which "Americans would hesitate to touch." In Geneva, he spent some time with

Dr. Lombard who considered iodine internally and externally a specific for the endemic goiters of Switzerland. Dr. Lombard had seen but one patient operated upon for goiter and he had died from "tetanus."[1]

Upon his return, he moved to Buffalo to become Professor of Surgery in the Medical School which opened in 1847. His colleagues included Austin Flint and James White, the first American to teach obstetrics by clinical methods. They were later joined by John Dalton, the great physiologist, and formed, according to Cushing, "as notable a faculty of energetic young men who could be found anywhere."[2]* These men, in addition to professorial duties and private practices, found time to publish the *Buffalo Medical Journal* which adequately documents their activities.

Not long after this journal started, the first event which was to change the field of surgery occurred, and within several months of the first use of ether in Boston, an editorial, probably by Flint, appeared describing the event and intimating that the agent was ether. A few months later in July, 1847, Hamilton reported his first use of ether anesthesia:

> *1st Case.*—John Harrington, aged 50; of a herculean frame and with powerful muscles had his left humerus dislocated into the axilla on the sixth of July. On the 16th, ten days after the accident, he called upon me, and in presence of Drs. John Trowbridge, Garvey, Dudley, Harvey and others, I made attempts at reduction as follows:
>
> First attempt.—Applied the compound pulleys, and extended the arm with as much force as would be prudent, fifteen minutes—arm at right angles with the body—rotating the arm occasionally during this time.
>
> Second.—Extended the patient upon the floor, and drew the arm in line of body, having my heel in the axilla (without pulleys).
>
> Third.—Patient lying in the same position, I pulled the arm at right angles with the body.
>
> Fourth.—Patient still extended, I adopted Malgaigne's method, pulling upward, with my foot upon the top of the shoulder.
>
> Fifth.—Patient seated on a chair, I drew the arm down over my knee, which rested in the axilla.
>
> Sixth.—Bled him twenty-four ounces, and until partial syncope was induced, and then tried again the second position.
>
> Seventh.—Repeated the first attempt during ten minutes, and now, while the extension was kept up fully, I made him respire sulphuric ether until he was completely intoxicated and insensible.
>
> Eighth.—Before the influence of the ether had begun to subside, the band to which the pulleys were attached broke, I then brought the axilla over the knee (fifth position) and the bone was made to resume its place with great ease. The relaxation of his muscles was now very complete. John said the ether was the best grog he ever took.
>
> Immediately after reducing this arm, I went with Dr. Dudley to his office to witness the reduction of the same luxation in another patient.
>
> *Case 2d.*—Peter Starr, aged 45, Dutchman, very muscular, fell this morning on the upper end of humerus and produced a dislocation downwards into the axilla—right arm.

*It is interesting to note a total fund of $32,000 was sufficient to allow this development.

> Dr. Dudley with two other men had soon after made attempts at reduction, but without success. Dr. Dudley then determined to use the pulleys, and, at my suggestion, to assist their operation by the ether.
>
> Dr. D., applied the pulleys to the patient at eleven o'clock, four hours after the accident, and immediately Dr. Harvey commenced the administration of the ether; in about one minute after its full effects were obtained, the bone slipped into its place.
>
> The patient said he was as if asleep, and that he knew nothing of it: yet, during the extension he drew his face, as though suffering pain.[3, 4]

During his Buffalo period, Hamilton, with Warren of Boston and Mutter of Philadelphia, was recognized as an outstanding plastic surgeon. His plastic operations varied in extent from the removal of pterygia to excision of one-half the mandible for carcinoma of the jaw. It was in 1854 that he performed the first crossleg pedicle graft,[5] but he had apparently been considering it for some time. In 1847, he proposed to a 15-year-old boy with an indolent leg ulcer that a piece of skin from the opposite leg be placed on the ulcer. He stated that this was his own idea but that he would delay getting it patented until he saw how his Boston friends got along with *their* ether patent.

Fig. 1.—Frank Hamilton, M.D. (1813-1886.)

However, both the boy and his "worthless inebriate father" refused the operation and Hamilton later noted that the ulcer was still open in 1864.[6] It was not until 1854 that he had the opportunity to perform this operation. At this time, he did a crossleg pedicle flap graft and the patient, whose ulcer had existed for two years, obtained complete cure. Although this is the first crossleg pedicle graft recorded, Hamilton was more interested in the use of skin

graft to repair an ulcer, which he felt was a new use for a graft. From time to time, Hamilton reported the use of other pedicle grafts and also the use of some free full thickness skin grafts.

From the reports published by Hamilton in the fifties, it is possible to get an idea of his practice. The greater portion of it was the treatment of fractures and dislocations but ligation of the external iliac artery, common carotid artery, treatment of vesicovaginal fistulas, tonsillectomies, amputations of the penis for cancer, and mastectomy for cancer were all reported by him. It is interesting to note that Hamilton felt the simple increase in size of the tonsils was not an indication for their removal but that tonsillitis or bronchitis was. He avoided tonsillectomy in the presence of acute inflammation.[7] Like most surgeons of his time, his work and speculations were not entirely confined to surgery. When Buffalo had several cholera epidemics, he became very much interested in this

55

FEMUR.

MIDDLE THIRD—*Continued.*

No.	Age when it occurred.	Time since it occurred.	Sex.	Right or left side.	Character of the fracture.	TREATMENT.	RESULT. United or not.	When united.	Amount of shortening.	Remarks.	Perfect or imperfect.
54	6 y.		M.	R.	Simple	Gibson's and then Hamilton's straight splint.	U.	1 m.	½ in.	Slightly bent forwards and outwards.	Imp.
55	22 y.	2 m.	M.	R.	Simple		U.		2 in.	Much bent outwards at seat of fracture.	Imp.
56	36 y.	4 m.	M.		Simple	Straight splint.	U.		1 in.		Imp.
57	22 y.	2 m.	M.	R.	Simple	Flagg's straight splint.	U.	2 m.	½ in.		Imp.
58	8 y.	5 y.	M.	L.	Simple	Double inclined plane.	U.		½ in.		Imp.
59	5 y.	11 d.	M.	L.	Simple	Side splint only.	U.	11 d.	¾ in.		Imp.
60	40 y.	2 m.	M	L.	Simple	Straight splint.	U.	3 w.	¼ in.		Imp.
61	22 y.	9 w.	M.	R.	Simple	Straight splint.	U.		¾ in.		Imp.
62	13 y.	13 y.	M.		Simple		U.		1½ in.	No halt; spine crooked.	Imp.
63	15 y.	19 y.	M.	L.	Simple		U.		¼ in.		Imp.
64	16 y.	25 y.	M.	L.	Simple		U.		¾ in.	No halt.	Imp.
65	30 y.	5 y.	M.	L.	Simple		U.		1¼ in.		Imp.
66	25 y.	17 w.	M.	L.	Simple	Straight splint.	U.		¾ in.	Upper fragment on inside of lower.	Imp.
67	30 y.	1 y.	M.	L.	Simple	Double inclined plane.	U.		¾ in.	Some bent outwards at seat of fracture.	Imp.
68	7 y.	6 w.	M.		Simple	Gibson's straight splint 2 weeks, and then Hamilton's.	U.	39 d.	¼ in.		Imp.
69	40 y.	4 y.	M.	R.	Simple	Double inclined plane.	U.	6 w.	1 in.	Bent forwards at seat of fracture.	Imp.
					mple	Desault's				ing of limb from	

Fig. 2.—A portion of one of Hamilton's Fracture Tables (1855).

disease and noted that the disease probably had a connection with excavations as the incidence was highest where sewers were being dug—probably a correct observation if an inaccurate deduction.[8] His interest in cholera apparently persisted, for, in 1866, he offered to take charge of a New York Welfare Hospital where an epidemic of the disease occurred. He believed that he aborted the disease by a program which included disinfection of ejecta by the use of phenol.[9]

During Hamilton's Buffalo period, his outstanding accomplishment, at least to his contemporaries, was his work on fractures. He began in 1853 to publish Fracture Tables, which were long-term follow-up reports on fracture cases, published not only for their scientific value but also because he felt that many of the malpractice suits of this litigious era were being decided on invalid evidence. Hamilton pointed out that many of the witnesses for the prosecution were excessively glowing in their claims which resulted in a verdict unfair to the physician. Hamilton's Tables were unbiased evidence which indicated what could be considered a good result in good hands at that time. The American Medical Association appointed Hamilton to investigate the frequency of deformities in fractures and, in 1855 and 1856, he read papers on this subject at the American Medical Association Convention.[10] Later these lectures were published as a book and also formed the basis of Hamilton's book on fractures which was the first exclusively devoted to this subject in the English language. Hamilton's book on Fractures and Dislocations appeared in 1859. Perhaps not much of this book might appear timely to us but the following paragraph indicates that gentleness in tissue handling is not entirely a recent development:

> I cannot dismiss the subject without calling attention to the necessity of exercising care and gentleness as well as skill in the examination of broken limbs. Nothing in my opinion betrays a lack of judgment as well as of common humanity on the part of the surgeon, so much as a rude and reckless handling of a limb already pricked and goaded into spasms by the sharp points of a broken bone. It is not enough to say that such rough manipulation is generally unnecessary; it is positively mischievous provoking the muscles to more violent contractions; increasing the displacement and not unfrequently producing a complete separation of impacted, denticulated, transverse or partial fractures which can never afterwards be wholly remedied; augmenting the pain and not unfrequently, I have no doubt, determining the occurrence of suppuration, gangrene, and death.

He recommended that a careful history be elicited, the patient reassured that he would not be hurt unnecessarily, then a most careful examination of the limb for abrasions, discoloration, and swelling. Following this, the surgeon was to use "the harsher means of touch and manipulation. Then the limb may be measured." Finally, if any doubt remained, the limb must be firmly held while the necessary manipulations were performed for the purpose of ascertaining the existence of mobility and of crepitus. Hamilton stated that he did not hesitate to use anesthesia to make the examination. The use of starch bandages was recommended for immobilization but the danger of gangrene from excessive tightness and deformity from looseness as the swelling subsides was stressed. The recent innovation of plaster of paris splints was viewed as much more satisfactory—a padded type of cast was recommended and the need for avoiding wrinkles was recognized.

In 1859, Hamilton followed Flint to Long Island College of Medicine where he became Professor of Surgery. Upon the outbreak of the Civil War, Hamilton became a volunteer regimental surgeon but rose rapidly to the rank of Lieutenant Colonel—one of four or five to reach that rank. In 1863, he

resigned from the Army and, a year later, he published a book based on his Union Army experience entitled *Military Surgeon*. Numerous case reports indicated the high mortality of all wounds as a result of infection and a large section was devoted to hospital gangrene. In a chapter on Tetanus, which was also a major menace, Hamilton stated that control of the convulsions was the essential problem and noted that woorari (curare) had been suggested, but in later works Hamilton mentioned only the use of opiates. He recommended that abdominal wounds should be treated by complete rest and decried recent, more radical French ideas. LeGouest had recently recommended that the wound of entry be enlarged and a finger thrust in the abdomen to see if perforation had taken place. Hamilton, however, demonstrated on dead subjects that there were usually from five to seven perforations as a result of small arms fire and felt that an effort to find and close all of these would inevitably prove fatal.

Upon his return from the war, Hamilton was made Professor of Military Surgery at Bellevue and was later made Professor of Surgery in 1868. In the next decade, he became one of New York's outstanding surgeons although he continued his especial interest in fractures. He produced in 1872 a text of surgery which, like his fracture book, became a standard work and went through a number of editions. Perhaps the most interesting portion of his text is the twelve pages (of the nine hundred and thirty) devoted to cancer. Hamilton pointed out that there was increasing evidence that cancer was epithelial in origin and that Billroth no longer thought that the numerous round cells were a primary feature of the disease. Under epithelial cancer, Hamilton stated:

> There are three points in the preceding brief account of the origin, progress, and nature of epithelioma which ought to serve as guides to treatment: First, that the disease . . . is at first essentially local; second, that it is infectious or capable of propagation through the system; third, that prolonged local irritation ranks among the most active causes in its production. Clinical experience confirms that epitheliomata have seldom returned which have been removed by the knife and in which a considerable amount of healthy tissue has been excised, including what might be called their entire atmosphere.

Under the headings hard cancer or scirrhus, medullary cancer, myxomatous cancer, various gross types were discussed and the "knife" recommended over caustics.

Hamilton's appearance before the nonmedical public as one of Garfield's surgeons—the other being Agnew of Philadelphia—has considerable interest. It is apparent that immediately after Garfield's shooting on July 2, 1881, a considerable number of Washington physicians who gathered on the confused scene became involved in the care of the President, who was the patient of D. W. Bliss. When the President unexpectedly survived the night, the staff was reorganized. Three physicians retired from the case and the two consultants were called in. Garfield had been shot from the rear so that the wound of entry was posteriorly located and probing had revealed that the

eleventh rib on the right had been fractured. Hamilton and Agnew saw the patient on the afternoon of the fourth of July and Bliss states,

> I gave them a detailed account of the explorations made in the wound and the unsettled convictions as to the course of the missile and the organs involved in the injury. They individually examined the wound with great care. These examinations consisted in the introduction of probes, flexible bougies in order to determine the course of the ball. With the evidences developed by this personal examination, together with the complete history of the shooting of the President and the progress of the symptoms for the first forty-seven hours, they proceeded to discuss the possible course of the ball and organs involved, that is, whether it passed directly forward into or through the liver, or was deflected backward at a right angle so as to involve the spinal column, or downward behind the peritoneum toward the pelvic cavity. Carefully weighing all the evidences, the more prominent symptoms upon which the diagnosis was based are presented in the following order: The relative position of the assassin to the President at the time of the shooting, the direction of the ball through the tissues, so far as safe exploration could determine, gradual subsidence or modification of pain and hyperaesthesia of the feet and scrotum; the repeated unsuccessful efforts to pass a probe or flexible instrument more than one-half inch in any direction beyond the fractured rib, except in a direction downward, a little forward and anterior to the twelfth rib, a distance of about two inches. The fact also was considered that explorations had twice been made with the finger—one by myself soon after I reached the injured President, and subsequently by Surgeon-General Wales of the Navy, on the occasion of the consultation on the evening of July 2d; and in each instance it was found impossible to successfully explore by that means beyond the inner border of the fractured rib so as to determine, with accuracy, the course of the ball, or even the condition of the tissues indicated by the end of the finger. Nor did they underestimate the significance of the profound shock, nor the unusual period of collapse which followed and seemed to point to extensive lesion of important viscera. However, that the kidneys, intestines, and peritoneum were not immediately involved, was made patent by the unrestrained passage of normal urine at proper intervals, the spontaneous movement from the bowels of natural faeces, the frequent discharge of flatus, and the absence of other symptoms of peritonitis. With all these facts before them it was impossible to determine positively the course taken by the ball. The indications pointed to a downward course of the ball into the pelvic cavity.[12]

(The decision was to adopt a conservative course.)

Almost immediately, the President's case became a sort of national clinical conference. An unnamed American telegraphed to Marion Sims for advice, who cabled back that "if the President had recovered from his shock and there is undoubted evidence that the ball has traversed the peritoneal cavity, his only safety is in opening the abdomen, cleaning out the peritoneal cavity, tying bleeding vessels, suturing the wounded intestine, and treating the case as we would after an ovariotomy."[13] This advice was less than welcome to the old Civil War surgeons and Hamilton in *The New York Times* (July 5) said "opening the abdomen for a bullet is not the same as taking out an ovary." During the President's protracted course, much discussion took place in the medical and lay press. Numerous speculations as to the course of the bullet appeared. Weisse[14] fired bullets into a body to determine the effect of bone deflection and later performed dissections, based on these deflection experi-

ments, to determine possibilities as to the wound track. It is apparent that Hamilton encouraged these experiments and attended the dissection.

Probably the greater part of the advice given and criticisms made were not helpful. We find *The Medical Record* complaining editorially: "The bulletins furnish scarcely anything upon which medical men can base an intelligent opinion. We have no facts regarding the skin, tongue, excreta, body weight, character of the pulse, nor even whether the temperature given is that of the mouth, axilla, or rectum. It would be quite possible for the attending physicians to be more explicit and satisfactory."[15] An abscess occurring near the wound of entry was drained August 8, but the President continued febrile although well enough so that he requested that three more of his numerous physicians* be discharged from the case. Finally after the development of parotitis and possibly angina pectoris, the President suddenly collapsed and died. An autopsy was performed which showed that the bullet had remained in the retroperitoneal area after traversing the body of the first lumbar vertebra and a portion of the pancreas. The cause of death was thought to be a secondary hemorrhage from the splenic artery although this was later disputed as being an artefact from the undertaker's embalming. A subhepatic abscess was also present and a recent article has suggested that death may actually have been due to coronary thrombosis.[16] After the publication of the post-mortem findings, there was general agreement that the President had been correctly treated and Marion Sims publicly stated his belief that this was true.

We have seen that Hamilton quickly took up anesthesia in 1847 and it is interesting to observe his reactions to antisepsis. Although during the cholera epidemic in New York in 1866, Hamilton felt that he had controlled the disease in the hospital by a number of measures, the most important being treatment of the feces by phenol, he never became enthusiastic about Listerism. Halsted was placed on his service at Bellevue and it is apparent from his remarks that Listerism was not practiced on Hamilton's service. Indeed the final edition of his surgical text (1886) gave little indication of the importance of antisepsis. This, of course, was a typical reaction for an American surgeon of the time. Lister's biographer, Cuthbert Dukes,[17] stated that there was little interest in antisepsis until after Lister's address in this country in 1876. As late as the middle eighties, surgeons opposed to antisepsis "dominated and predominated" on the New York scene.[19]

Halsted, however, was influenced in other directions by Hamilton. He was much impressed by his frequent and conscientious rounds at Bellevue. Hamilton pointed out to Halsted that the greatest satisfaction he would ever obtain from his profession would be in original work. This stimulus apparently led to several of Halsted's early papers which were on fracture methods. Many years later, Halsted recalled that Hamilton always arrived at Bellevue riding a gray horse and wearing spurs.[19]

*When he was shot during the 1912 Presidential Campaign, Theodore Roosevelt, possibly unfavorably impressed by the results obtained by the numerous physicians in the McKinley and Garfield cases, insisted on having but one physician—John B. Murphy.

During the last several years of his life, Hamilton developed repeated pulmonary hemorrhages, which his old colleague, Austin Flint, believed to be the result of phthisis. In 1886, as a result of this progressive pulmonary ailment, he died.

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Book Reviews

Wiederherstellungschirurgie des Gesichts. By Prof. Dr. Reinhard Perwitzschky, Direktor der Hals-, Nasen-, Ohrenklinik der Ehemals Deutschen Universitat Breslau. Pp. 228, with 176 illustrations. Berlin, 1951, W. de Gruyter & Co. DM 34.

This is a scholarly treatise on maxillofacial plastic surgery, based mainly upon a large experience with war injuries. There is a good bibliography, predominantly from the European literature, and the book itself is written in German. While offering little that is new, the field is thoroughly covered and several facets are outstanding.

There is a fine section on the neuroanatomy of this region and the application of local anesthesia. The author makes extensive use of flaps from adjoining tissue, and at times would seem to have gone too far in this direction to the detriment of the donor areas. However, the basic principles of advancement and rotation flaps are well covered and beautifully illustrated by a large collection of unusually clear photographs, accompanied where indicated by equally clear diagrams.

The work is in sufficient detail to be of value to the casual operator in this field, and the large amount of clinical material presented makes the book one of interest to the specialist.

Blutgruppenbestimmung und Bluttransfusion. By Peter Dahr and E. Regenbogen. Ed. 2. Pp. 256. Stuttgart, 1952, Georg Thieme Verlag. DM 16.50. Agent for U. S. A.: Grune & Stratton, Inc., New York, N. Y.

The authors have intended this book to serve as a guide to the procedures of blood group determinations and blood transfusions. It is divided into two parts: The first half, written by Dahr, deals with untoward reactions of blood transfusions and means of avoiding them; the second part, written by Regenbogen, describes the techniques, indications, and contraindications for blood transfusions. The book stresses technical and administrative detail rather than the fundamental principles of the methods described. The theoretical parts are intertwined with historic and practical aspects in such a way that we would judge it difficult for the uninitiated reader to gain a clear working concept of the present status of the subject. Although the authors recognize the importance of careful Rh typing, the book contains only a short reference to the Coombs' test and makes no mention of the services which it can render in the differential diagnosis of acquired and congenital hemolytic anemias. Also, no mention is made of the lifesaving potentialities of the artificial kidney in transfusion reactions, and the authors suggest renal decortication instead. Otherwise, however, the book discusses the same topics which are considered germane to its field in the United States, and it does so with competence. To the American physician who is interested in some of the everyday problems confronting his German colleague, Dahr and Regenbogen's exposition should make interesting reading. One may infer that blood banks and their concomitant conveniences are still somewhat of a rarity in Germany, even today, and one gathers that the German blood donor finds himself entangled in a veritable maze of regulations set up by his government.

Postgraduate Lectures, Volume IV. By Arthur Steindler, M.D., F.A.C.S., Professor of Orthopedic Surgery, University of Iowa, Iowa City, Ia. Pp. 308, with 276 illustrations. Springfield, Ill., 1952, Charles C Thomas. $9.75.

In this, the fourth volume of his postgraduate lectures, Dr. Steindler has maintained the same high level of style, content, and lucidity which distinguished the preceding volumes. At a time when the tendency in the treatment of arthritis is to rely upon some magic drug or formula, it is refreshing to read a clear statement of the many time-tested methods which can bring relief and which must be utilized, if only as adjuncts, if any treatment is to succeed. The remainder of the volume is taken up with discussions of muscular diseases, gout, osteoporosis, and avitaminosis, among others. Each section is accompanied by a bibliography of significant articles. These bibliographies are valuable tools for scholarship in their own right.

Dr. Steindler and the publishers should be proud of these volumes which belong in the libraries of all physicians treating diseases of the musculoskeletal system.

Handbook of Operative Surgery: Surgical Gynecology. By J. P. Greenhill, M.D., Professor of Gynecology, Cook County Graduate School of Medicine, Attending Gynecologist, Cook County Hospital, Attending Obstetrician and Gynecologist, Michael Reese Hospital, Chicago, Ill. Pp. 350, with 101 illustrations—by Angelo Bartenbach. Chicago, 1952, Year Book Publishers, Inc. $8.50.

The author states that this book is primarily for young gynecologists, general surgeons, and those physicians in general practice who also perform operations.

The first section outlines the preoperative preparation, postoperative care, and complications in gynecological surgery. The remainder of the book is essentially an atlas of a wide range of gynecological operations being performed today.

The operations are discussed in a concise, step-by-step manner, and the description in the text is supplemented by clear illustrations which appear on the opposing page to the text for easy reference.

In addition, operative procedures such as bowel resection and hernia repair, which occasionally must be done by the gynecological surgeon, are discussed.

Handbook of Operative Surgery of the Chest. By Julian Johnson, M.D., D.Sc. (Med.), Professor of Surgery, and Charles K. Kirby, M.D., Assistant Professor of Surgery, School of Medicine, University of Pennsylvania, Philadelphia, Pa. Pp. 387, with 81 illustrations—by Edna Hill. Chicago, 1952, Year Book Publishers, Inc. $9.00.

The authors state in the preface that this book is primarily an atlas of thoracic surgical operations. As such it leaves out any discussion of differential diagnosis, etiology, and pathology of the disease for which the surgery is outlined. Although concise, the book is very wide in its scope leaving little to the imagination. The basic points of surgical physiology of the thorax are discussed as well as special diagnostic studies, the principles involved in pre- and postoperative care, and special problems arising during thoracic operations such as cardiac arrest.

A very wide range of operations is outlined, step by step, according to well-accepted present-day techniques. These include, not only pulmonary procedures, but also operations on the heart and great vessels, and on the upper gastrointestinal tract.

The illustrations are quite clear. These illustrations and the text discussing them are on opposite pages so that ready reference is possible.

The book can be recommended to students of all levels, especially those in general surgery wishing to extend their knowledge of thoracic surgical procedures.

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers as space permits.

SURGICAL GYNECOLOGY. By J. P. Greenhill, M.D., Professor of Gynecology, Cook County Graduate School of Medicine, Obstetrician and Gynecologist, Cook County Hospital, Obstetrician and Gynecologist, Michael Reese Hospital. Price $8.50. Pp. 350, with 101 illustrations. Chicago, 1952, The Yearbook Publishers, Inc.

INJURY OF THE XIPHOID. By Michael Burman, M.D., and Samuel E. Sinberg, M.D. Price $3.50. Pp. 92, with few illustrations. New York, 1952, Columbia University Press.

AMBULATORY PROCTOLOGY. By Alfred J. Cantor, M.D., Proctologist, Kew Gardens Hospital, Long Island, N. Y., formerly Assistant Attending Gastroenterologist, Queens General Hospital and Assistant Adjunct Proctologist, Hospital for Joint Diseases, New York. Price $10.00. Pp. 557, with 382 illustrations. New York, 1952, Paul B. Hoeber, Inc.

HISTORY AND DEVELOPMENT OF NEUROLOGICAL SURGERY. By Ernest Sachs, A.B., M.D., Research Associate in Physiology, Yale University, New Haven; formerly Professor of Clinical Neurological Surgery, Washington University School of Medicine, St. Louis, Mo. Price $5.00. Pp. 158, with few illustrations. New York, 1952, Paul B. Hoeber, Inc.

ANURIE BIE CHROMOPROTEINURIE. By Professor Dr. H. U. Zurich. Price DM 14.70. Pp. 138, with few illustrations. Germany, 1952, Richard Bechtle.

SURGERY OF THE CHEST. By Julian Johnson, M.D., Professor of Surgery, School of Medicine and Graduate School of Medicine, University of Pennsylvania, and Charles K. Kirby, M.D., Assistant Professor of Surgery, School of Medicine, University of Pennsylvania. Price $9.00. Pp. 387, with 81 illustrations. Chicago, 1952, The Yearbook Publishers, Inc.

LEHRBUCH DER RONTGENDIAGNOSTIK. By H. R. Schinz, M.D., W. E. Baensch, M.D., E. Friedle, M.D., and E. Vehlinger, M.D. Price not given. Pp. 338, with 4,221 illustrations. Stuttgart, 1952, Georg Thieme Verlag, Agent for U.S.A.: Grune & Stratton, Inc., New York, N. Y.

DIE OSTEOMALAGIE. By Dr. Markus Wernly. Price DM 14.40. Pp. 101, with few illustrations. Stuttgart, 1952, Georg Thieme Verlag, Agent for U.S.A.: Grune & Stratton, Inc., New York, N. Y.

LEHRBUCH DER RONTGENDIAGNOSTIK. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. Price not given. Pp. 138. Stuttgart, 1952, Georg Thieme Verlag, Agent for U.S.A.: Grune & Stratton, Inc., New York, N. Y.

BATTLE CASUALTIES. By Gilbert W. Beebe, and Michael E. De Bakey, M.D. Price $10.50. Pp. 277, with few ilustrations. Springfield, Ill., 1952, Charles C Thomas, Publisher.

ALLGEMEINE UND SPEZIELLE CHIRURGISCHE OPERATIONSLEHRE ZEVEITE AUFLAGE. By Dr. Rudolph Zenker, Director of Chirurgischen Klinik der University. Price not given. Pp. 868, with 556 illustrations. Berlin, 1951, Springer-Verlag.

BASIC MEDICAL PHYSIOLOGY. By W. B. Youmans, Ph.D., M.D., Professor of Physiology, University of Wisconsin. Price $7.50. Pp. 436, with 116 illustrations. Chicago, 1952, The Yearbook Publishers, Inc.

CLINICAL PROBLEMS IN CANCER RESEARCH. Sloan-Kettering Institute Seminar. David Karnofsky, Chairman Seminar Committee. Pp. 194, with 7 illustrations. New York, 1952, Sloane-Kettering Institute.

PHYSICAL FOUNDATIONS OF RADIOLOGY. By Otto Glasser, Edith H. Quimby, Lauriston S. Taylor, and J. L. Weatherwax. Price $6.50. Pp. 581, with 112 illustrations. New York, 1952, Paul B. Hoeber, Inc.

EMERGENCY SURGERY. Volume IV. By Hamilton Bailey, M.D. Price $25 for five-piece set. Pp. 750, with 1,171 illustrations. Baltimore, 1952, Williams & Wilkins Company.

BRAIN SURGEON: AUTOBIOGRAPHY OF DR. WILLIAM SHARPE. By Dr. William Sharpe. Price $3.75. Pp. 271, with no illustrations. New York, 1952, Viking Press, Inc.

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